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**Managing the Tension Between Knowledge
Exploration and Exploitation:
The Case of UK Biotechnology**

By
Peter Mc Namara

Presented in fulfilment of the requirements of the:
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Department of Strategy and Marketing

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS

.....	14
-------	----

DEDICATION

.....	16
-------	----

ABSTRACT

.....	17
-------	----

CHAPTER ONE

INTRODUCTION

RESEARCH QUESTIONS.....	20
-------------------------	----

1. FROM A THEORETICAL PERSPECTIVE, WHAT IS THE KNOWLEDGE EXPLORATION/EXPLOITATION DILEMMA?..... 20
2. IS THERE EVIDENCE WITHIN A REAL ORGANISATIONAL CONTEXT THAT A FIRM'S ACTIVITIES CAN BE EXPLAINED THROUGH THE CONCEPTUAL LENS OF BALANCING A TENSION BETWEEN KNOWLEDGE EXPLORATION AND EXPLOITATION? 21
3. DO THE FINANCIAL MARKETS REWARD ANNOUNCEMENTS OF EXPLOITATION ACTIVITIES WITH HIGHER RETURNS THAN EXPLORATION ACTIVITIES, AS PREDICTED BY THEORY?..... 22

INDUSTRIAL CONTEXT	23
--------------------------	----

- BIOTECHNOLOGY DEFINED 23
- APPLICATIONS OF BIOTECHNOLOGY AND REGULATION..... 24
- PATENTS: THE REWARD FOR HIGH RISKS AND COSTS OF REGULATORY APPROVAL..... 25
- BIOTECHNOLOGY AND THE PHARMACEUTICAL SECTOR..... 28

SAMPLE SELECTION	32
UK BIOTECHNOLOGY AND THE TENSION BETWEEN EXPLORATION AND EXPLOITATION ACTIVITIES	32
SELECTION OF SAMPLE COMPANIES	33
STRUCTURE OF THESIS.....	36

CHAPTER TWO

THE ANTAGONISTIC NATURE OF KNOWLEDGE MANAGEMENT:

THE BALANCE BETWEEN KNOWLEDGE EXPLORATION AND EXPLOITATION

INTRODUCTION	45
CONTRIBUTION OF THIS CHAPTER	48
STRUCTURE OF THIS CHAPTER	49
EXPLORATION/EXPLOITATION AS A TRIAD: EXPLORATION, DEVELOPMENT AND USE FOR APPROPRIATION	51
EXPLORATION.....	51
DEVELOPMENT	53
<i>The link between Exploration and Development.....</i>	<i>54</i>
<i>Distinguishing Development from Use for Appropriation</i>	<i>58</i>
USE FOR APPROPRIATION	59
PROPOSITIONS: VALUE ADDED AND KNOWLEDGE EXPLORATION EXPLOITATION.....	61
NONAKA'S KNOWLEDGE SPIRAL AND EXPLORATION/EXPLOITATION	64
ANTAGONISTIC PROCESSES.....	67
CORE RIGIDITIES	67
SLOW RATE OF LEARNING.....	68
IMITATION	70
COMPLEMENTARITY OF ANTAGONISTS.....	71
SOME PIVOTAL CHARACTERISTICS IN THE ANTAGONISTIC NATURE OF KNOWLEDGE MANAGEMENT	72
MOVEMENTS BETWEEN THE PROCESSES OF EXPLORATION AND CORE RIGIDITY (FIGURE TWO) ..	72
<i>Mavericks</i>	<i>74</i>
<i>Personnel Turnover.....</i>	<i>75</i>
<i>Unlearning</i>	<i>76</i>

MOVEMENTS BETWEEN THE PROCESSES OF DEVELOPMENT AND SLOW RATE OF LEARNING (FIGURE THREE)	77
<i>Slack</i>	79
<i>Common Codes and Shared Language</i>	81
<i>Experimentation</i>	82
MOVEMENTS BETWEEN THE PROCESSES OF USE FOR APPROPRIATION AND IMITATION (FIGURE FOUR)	83
COMPLEMENTARITY AND ANTAGONISM BETWEEN CHARACTERISTICS.....	87
CONCLUSION	88

CHAPTER THREE

BALANCING KNOWLEDGE EXPLORATION AND EXPLOITATION IN A REAL ORGANISATION OVER TIME:

LESSONS FROM THE CELLTECH CASE

INTRODUCTION	97
THEORY	98
METHODS AND DATA COLLECTION	101
SOURCES OF DATA, VALIDITY AND RELIABILITY	101
THE INTERVIEW PROCESS	102
CLASSIFICATION OF ACTIVITIES AS EXPLORATION AND EXPLOITATION.....	104
AN OVERVIEW OF CELLTECH	107
EXPLORATION/EXPLOITATION AS A LENS IN UNDERSTANDING CELLTECH'S RENEWAL	110
EXPLORATION EXPLOITATION INSIDE THERAPEUTICS	112
FROM CORE RIGIDITIES TO EXPLORATION FOR NEW CORE CAPABILITIES: ACTIONS TAKEN TO PROMOTE EXPLORATION AND EXPLOITATION INSIDE CELLTECH	116
CREATING A CRISIS	117
UNLEARNING, REORGANISING AND NEW RECRUITS.....	119
SYSTEMS TO FOSTER THE COEXISTENCE OF EXPLORATION AND EXPLOITATION	121
COMMON CODES AND SHARED LANGUAGE.....	122

EXPLORATION AND EXPLOITATION OF A COLLABORATIVE CAPABILITY	123
DISCUSSION.....	124
CONCLUSIONS.....	129

CHAPTER FOUR:

WEALTH EFFECTS OF ANNOUNCEMENTS ON EXPLORATION AND EXPLOITATION EVENTS AMONGST UK THERAPEUTIC BIOTECHNOLOGY FIRMS

INTRODUCTION	134
A WHISTLE-STOP TOUR OF THE PREVALENCE OF EVENT EFFECTS	138
BRIEF EXPLANATION OF WHAT AN EVENT STUDY DOES.	138
SOME EVENT STUDIES IN THE MANAGEMENT AND FINANCIAL ECONOMICS LITERATURE.....	139
THE 'JANUARY EFFECT', IPOs AND STOCK SPLITS: A CHALLENGE TO AN EFFICIENT MARKET HYPOTHESIS?	142
THEORY AND HYPOTHESIS	145
ALLIANCES AND WEALTH CREATION	145
PROGRESS IN THE R&D PROCESS	158
HIERARCHY OF SHAREHOLDER WEALTH EFFECTS: APPROPRIATION, DEVELOPMENT AND EXPLORATION.....	161
METHODOLOGY	163
EVENT AND SAMPLE DEFINITION.....	163
CALCULATION OF ACTUAL, NORMAL AND ABNORMAL RETURNS.....	165
EVENT WINDOWS AND CUMULATING ABNORMAL RETURNS.....	169
CONTROL FOR CONFOUNDING EVENTS.....	172
DATA ANALYSIS.....	173
IMPACT OF ALLIANCE ANNOUNCEMENTS UPON SHAREHOLDER WEALTH.....	173
IMPACT OF ANNOUNCEMENTS OF PROGRESS IN R&D UPON SHAREHOLDER WEALTH.....	176
IS THERE A HIERARCHY OF SHAREHOLDER WEALTH EFFECTS?.....	180
ABSOLUTE CHANGE AS DISTINGUISHED FROM ABNORMAL RETURNS	181
DISCUSSION AND CONCLUSIONS	185

CHAPTER FIVE

CONCLUSIONS

THE MAIN FINDINGS OF THIS THESIS: RESEARCH QUESTIONS RE-VISITED	212
RELATING THE FINDINGS OF CHAPTER TWO TO THE RESEARCH QUESTION ONE.....	212
RELATING THE FINDINGS OF CHAPTER THREE TO RESEARCH QUESTION TWO	218
RELATING THE FINDINGS OF CHAPTER FOUR TO RESEARCH QUESTION THREE.....	221
REFLECTIONS ON THE CONNECTIONS BETWEEN THE FINDINGS OF CHAPTERS TWO, THREE AND FOUR	227
LIMITATIONS OF THIS STUDY	228
SMALL SAMPLE SIZE	228
SECTOR BIAS.....	231
OPERATIONALISATION.....	231
IMPLICATIONS OF FINDINGS UPON THE LITERATURE AND MANAGEMENT POLICY	232
TEMPORALLY DISTANT EXPLORATION ACTIVITIES CAN ADD OBSERVABLE SHAREHOLDER VALUE	233
SMALL COMPANY LISTINGS COULD OFFER BENCHMARKS FOR REWARDING STAFF, INVOLVED IN EXPLORATION AND DEVELOPMENT PROJECTS INSIDE LARGE FIRMS	236
ALLIANCE FORMATION PLAYS AN IMPORTANT ROLE IN SIGNALLING THE VALUE OF EXPLORATION AND DEVELOPMENT ACTIVITIES	239
REFERENCES	244

LIST OF TABLES

CHAPTER ONE

TABLE ONE: THE DRUG DISCOVERY AND DEVELOPMENT PROCESS	37
TABLE TWO: SIZE OF THE PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRY IN 1998	38
TABLE THREE: THE SIZE OF GLOBAL BIOTECH – EUROPEAN AND USA BIOTECHNOLOGY SECTORS COMPARED TO GLAXO WELLCOME	39
TABLE FOUR: NUMBER OF BIOTECHNOLOGY FIRMS: EUROPE VERSUS USA	40
TABLE FIVE: NUMBER OF EUROPEAN BIOTECHNOLOGY FIRMS BY COUNTRY	40
TABLE SIX: EQUITY RAISED BY BIOTECHNOLOGY FIRMS: EUROPE VERSUS USA	41
TABLE SEVEN: BIOTECHNOLOGY FIRMS ALLIANCE ACTIVITY	41
TABLE EIGHT: PERFORMANCE OF UK QUOTED THERAPUTICS BIOTECHNOLOGY FIRMS	42

CHAPTER FOUR

TABLE ONE: PERCENTAGE DAILY ABNORMAL RETURNS FOR ALL EVENTS	192
<u>PANEL A</u> : PRESTIGE ALLIANCES (N=15)	192
<u>PANEL B</u> : PHASE II III TRIALS (N=16)	192
<u>PANEL C</u> : REGIONAL ALLIANCES (N=15)	193
<u>PANEL D</u> : DISCOVERY AND PHASE I TRIALS (N=8)	193
TABLE TWO: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR ALL ALLIANCES (N=31)	194
TABLE THREE: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR PRESTIGE ALLIANCE (N=15)	195
TABLE FOUR: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR REGIONAL ALLIANCE (N=16)	196

TABLE FIVE: PERCENTAGE CUMULATIVE ABNORMAL RETURNS: DISCOVERY, PHASE I, II AND III TRIALS (N=24)	197
TABLE SIX: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR PHASE II AND III TRIALS (N=16)	198
TABLE SEVEN: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR DISCOVERY AND PHASE I TRIALS (N=8)	199
TABLE EIGHT: RESULTS OF DUMMY REGRESSION MODEL	200
TABLE NINE: ABSOLUTE CHANGE IN MARKET CAPITALISTION FOR PRESTIGE ALLIANCES (DAY 0 LESS DAY -1)	201
TABLE TEN: ABSOLUTE CHANGE IN MARKET CAPITALISTION FOR PII/III CLINICAL TRIALS (DAY 0 LESS DAY -1)	202
TABLE ELEVEN: ABSOLUTE CHANGE IN MARKET CAPITALISTION FOR REGIONAL ALLIANCES (DAY 0 LESS DAY -1)	203
TABLE TWELVE: ABSOLUTE CHANGE IN MARKET CAPITALISTION FOR DISCOVERY AND PI CLINICAL TRIALS (DAY 0 LESS DAY -1)	204
TABLE THIRTEEN:SUMMARY OF PAST EVENT STUDIES OF JOINT VENTURES AND ALLIANCES	205
TABLE FOURTEEN: A HIERARCHY OF WEALTH CREATION	207

CHAPTER FIVE

TABLE ONE: EVENT STUDY HYPOTHESIS REVIEWED	242
TABLE TWO: SUMMARY OF IMPLICATIONS	243

LIST OF FIGURES

CHAPTER TWO

FIGURE ONE: BALANCING THE EXPLORATION/EXPLOITATION DILEMMA AS A TRIAD OF ANTAGONISTIC PROCESSES	92
FIGURE TWO: THE ANTAGONISTIC NATURE OF KNOWLEDGE EXPLORATION	93
FIGURE THREE: THE ANTAGONISTIC NATURE OF KNOWLEDGE DEVELOPMENT	94
FIGURE FOUR: THE ANTAGONISTIC NATURE OF APPROPRIATING A RETURN FROM KNOWLEDGE.....	95
FIGURE FIVE: AN ANTAGONISTIC SYSTEM OF KNOWLEDGE MANAGEMENT	96

CHAPTER THREE

FIGURE ONE: INPUT MEASURES OF EXPLORATION/EXPLOITATION BALANCE: ALLOCATION OF RESOURCES	130
FIGURE TWO: PERFORMANCE OF CELLTECH BIOLOGICS	131
FIGURE THREE: OUTPUT MEASURES OF EXPLORATION EXPLOITATION BALANCE: REVENUE	132
FIGURE FOUR: BALANCING EXPLORATION AND EXPLOITATION IN THERAPEUTICS	133

CHAPTER FOUR

FIGURE ONE: DAILY ABNORMAL RETURNS FOR ALL EVENTS (mean adjusted returns model)	208
FIGURE TWO: CUMULATIVE ABNORMAL RETURNS FOR ALL ALLIANCES AND ALL TRIALS (mean adjusted returns model)	209

CONTENTS OF APPENDICES

APPENDIX ONE

THE CELLTECH CASE STUDY:

CELLTECH'S REJUVENATION IN THE 1990s

INTRODUCTION	259
THE EARLY DAYS: CRISIS, A NEW TEAM, AND A NEW MANDATE	260
THE EMERGENCE OF A CRISIS.....	260
THE APPOINTMENT OF A NEW TEAM.....	263
SHAREHOLDERS AND THE NEW MANDATE	263
RE-STRUCTURING	265
THE EMERGENCE OF A NEW STRATEGIC FOCUS	266
RE-ORGANISING TEAMS FOR SCIENTIFIC CREATIVITY	269
INTER-DISCIPLINARY TEAMS.....	269
MOTIVATING SCIENTISTS TO CHANGE	270
INTR-DISCIPLINARY LEARNING.....	271
THE NEW STRATEGY IN ACTION: THE BAYER COLLABORATION	272
SELECTION OF THE PROJECT & EARLY DAYS.....	272
COLLABORATION - MAKING A DEAL	274
LEARNING AND ADAPTATION FROM CDP 571/BAYX1351.....	274
BUILDING ON EARLY COLLABORATIVE SUCCESS	277
SYSTEMS TO MAINTAIN MOMENTUM	279
RESEARCH REVIEW SYSTEMS	280
DEVELOPMENT REVIEW SYSTEMS	281
ANNUAL REVIEW SYSTEMS	282
STRATEGIC REVIEWING SYSTEMS.....	282
A BITTER SWEET PILL:	284
THE RESULTS OF THE SEPTIC SHOCK TRIALS	284
CELLTECH AND THE FUTURE.....	286

TABLE ONE: FINANCIAL SUMMARY OF CELLTECH PLC	288
TABLE TWO: BACKGROUND OF SOME OF CELLTECH'S EXECUTIVE TEAM	289
TABLE THREE: OVERVIEW OF CELLTECH'S PRINCIPAL PUBLICLY QUOTED RESEARCH AND DEVELOPMENT ACTIVITIES	290
TABLE FOUR: OVERVIEW OF SEVEN LEADING UK BIOTECH FIRMS	291
FIGURE ONE: CELLTECH'S NETWORK OF MAJOR COLLABORATORS	292
FIGURE TWO: PERFORMANCE OF CELLTECH VERSUS FTSE PHARMACEUTICALS MARKET INDEX.....	293
REFERENCES	294

APPENDIX TWO

THE POLYMASC CASE STUDY:

FORMATION, FLOTATION AND EARLY YEARS OF A NEW QUOTED UK BIOTECHNOLOGY FIRM

INSTITUTIONAL AND TECHNOLOGICAL HERITAGE	295
THE ROYAL FREE HOSPITAL SCHOOL OF MEDICINE, UNIVERSITY OF LONDON.....	295
POLYMASC'S TEAM, TECHNOLOGY AND THENCE ITS NAME.....	296
<i>The Founding Scientists</i>	297
<i>The Technology</i>	298
THE AIM FLOTATION	300
CONTEXT IN WHICH THE FIRM WAS FLOATED	300
IMPACT OF THE AIM LISTING.....	302
POLYMASC'S STRATEGY	304
TECHNOLOGICAL	304
<i>Building Patent Protection</i>	305
COMMERCIAL	306
STRATEGIC GOALS	306
FINANCIAL GOALS.....	308
ORGANISATIONAL DESIGN.....	309

MULTI-DISCIPLINARY TEAMS AND MERITOCRACY.....	309
'IDEAS MERCHANTS' AND 'HUMAN DATABASES'	311
MANAGING TENSION: MOTIVATION AND COMMUNICATION.....	312
MANAGEMENT OF ALLIANCES	316
GOAL AND FORM OF ALLIANCES	316
PARTNER IDENTIFICATION AND PURSUIT	317
CLOSING THE DEAL	321
OPERATIONAL MANAGEMENT OF ALLIANCES	324
MANAGING THE PIPER.....	325
CONCLUSION	327
TABLE ONE: MAJOR SHAREHOLDERS	329
TABLE TWO: OVERVIEW OF A SELECTION OF POLYMASC'S PATENTS	330
TABLE THREE: FINANCIAL SUMMARY OF POLYMASC PLC	331
TABLE FOUR: POLYMASC'S ALLIANCES	332
TABLE FIVE: POLYMASC COMPARED TO SOME BIOTECHNOLOGY FIRMS LISTED ON THE LONDON STOCK EXCHANGE.....	333
TABLE SIX: LIST OF POLYMASC EVENTS TO MARCH 1998 (as per Extel)	334
FIGURE ONE: PERFORMANCE OF POLYMASC'S SHARES RELATIVE TO A BASKET OF UK BIOTECHNOLOGY SHARES	335

APPENDIX THREE

THE OXFORD MOLECULAR CASE STUDY:

MANAGING INTER-ORGANISATIONAL COLLABORATIVE DRUG DISCOVERY PROJECTS

INTRODUCTION	336
COLLABORATIVE DISCOVERY'S STRATEGIC DIRECTION	341
COLLABORATIVE DISCOVERY'S FINANCIAL STRATEGY	344

WHY COLLABORATIVE PARTNERS COME TO THE DIVISION	346
MANAGING THE VIRTUAL FIRM AT COLLABORATIVE DISCOVERY	348
VIRTUAL COMPANY.....	348
INTER-DISCIPLINARY TEAM WORK.....	349
MANAGEMENT OF SUB-CONTRACTORS	350
CUSTOMER RELATIONS AND INTERACTIONS.....	352
YAMANOUCHI AND ALIZYME COLLABORATIONS	354
THE SUCCESS OF COLLABORATIVE DISCOVERY DIVISION	356
CONCLUSION	358
TABLE ONE: THE DRUG DISCOVERY PROCESS.....	360
TABLE TWO: BIO-INFORMATICS - IDENTIFICATION OF BIOLOGICAL TARGETS.	361
TABLE THREE: CHEMO-INFORMATICS - THE IDENTIFICATION OF LEAD COMPOUNDS.	362
TABLE FOUR: COMPUTER AIDED MOLECULAR DESIGN (CAMD) - LEAD OPTIMISATION	363
TABLE FIVE: MARKET FOR OUTSOURCED SPECIALIST DRUG DISCOVERY IT AND SERVICES	364
TABLE SIX: CAMBRIDGE COMBINATORIAL LTD (PRIVATE, UNLISTED, COMPANY)...	365
TABLE SEVEN: CAMBRIDGE DRUG DISCOVERY LTD (PRIVATE, UNLISTED, COMPANY)	366
TABLE EIGHT: COLLABORATIVE DISCOVERY DIVISION PUBLICLY DETAILED PROJECTS.....	367
TABLE NINE: COMPARATIVE OVERVIEW OF YAMANOUCHI AND ALIZYME	368
REFERENCES	369

APPENDIX FOUR

SAMPLE OF EVENTS INCLUDED AND EXCLUDED FROM EVENT STUDY

EVENTS INCLUDED IN STUDY	370
NUMBER OF EVENTS INCLUDED IN EVENT STUDY:.....	373
EVENTS EXCLUDED FROM EVENT STUDY DUE TO CONFOUNDING EVENTS	374
NUMBER OF CONFOUNDING EVENTS	377
EVENTS EXCLUDED DUE TO LACK OF ESTIMATION WINDOW DATA	378
NUMBER OF EVENTS EXCLUDED DUE TO LACK OF ESTIMATION PERIOD DATA	379
FAILURE EVENTS	380
NUMBER OF FAILURE EVENTS	380

APPENDIX FIVE

PAPERS PUBLISHED AND CONFERENCE PARTICIPATION

ACADEMIC JOURNAL PAPERS	381
CONFERENCE PAPERS.....	381
WORKING PAPER	382
TRADE JOURNAL PUBLICATIONS.....	382

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Dedication

In memory of the following family and friends:

Rose O'Regan (1999); Professor Jim Crowley (1999); Patrick Sheridan (1998); and
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gone but not forgotten.

And to the future, my closest friend, dearest companion, and wife, Madeleine.

Abstract

In prior literature it has been argued that there exists a tension between balancing investments in Exploration for new organisational knowledge against the Exploitation of current stocks. It is argued that over time firms tend towards an ever increasing focus upon Exploitation to the exclusion of investments in Exploration. It is argued that this bias is in part due to the causally complex feedback loops between Exploration activities and financial performance. The tendency for Exploitation to drive out Exploration activities over time is argued to pose a serious threat to firm's long term prosperity and survival.

This thesis first reviews and interprets the diverse literature on the tension between Exploration and Exploitation. This interpretation of prior work highlights that Exploitation is not a single process, but rather two: incremental Development of current stocks of knowledge and Appropriation of a return from those stocks through use and sale in the marketplace. It is argued that the classic tension between Exploration and Exploitation is intermediated by the process of Development, which seeks to convert new organisational knowledge into forms amenable to appropriation of a financial return, in addition to making incremental improvements to current stocks of organisational knowledge. It is argued that the tension between these three processes only exists in the short term. In the long term the success of each process is dependent upon the other two. It is argued, however, that in the long term it is difficult sustain individual efforts to extend the firm's knowledge stocks through Exploration, Development, or efforts to appropriate a return through use, due to the existence of three antagonistic processes that impede each of these three processes individually. These antagonists are Core Rigidities, Slow Rate of Learning and Imitation by competitors. Through the literature review insights are offered into how management can suppress these antagonistic processes.

Chapters Three and Four empirically study the phenomena of Exploration and Exploitation of organisational knowledge in the context of the UK therapeutics biotechnology sector. In Chapter Three an in-depth case study of a leading firm,

Celltech, is undertaken. From this case it is argued that contrary to prior literature it is possible for a firm to maintain a balance between Exploration and Exploitation beyond the short term. It is shown that Celltech's Exploration activities can be linked directly to the financial renaissance of the firm between 1990 and 1998. Insights are offered into how management sought to maintain this balance and ensure that the long term complementary relationship between the processes of Exploration, Development and Appropriation was not undermined by short-term actions.

Based on the experiences of Celltech and other biotechnology firms key quantifiable outputs of the processes of Exploration, Development and Appropriation are devised. Using an event study methodology, announcements of these key outputs, by all publicly quoted UK biotechnology firms between December 1995 and January 1999, are analysed. It is found that contrary to prior theoretic suggestions the outputs of both Exploration and Exploitation activities generate observable financial valuations in the stock market. Announcement of positive progress in Exploration and Development activities are found to coincide with increases in share price over and above either the past performance of the firm or the contemporary performance of market indices. This suggests that contrary to theoretical arguments in the literature the causal feedback loop between Exploration and Development activities and financial performance can be quite direct.

It is also found that alliance formation plays an important role in value creation. It is argued that the increase in market capitalisation that formation of alliances generate is not fully explained by the sharing of resources and capabilities alone. It is argued that formation of an alliance with a firm that has a high scientific and commercial reputation within the stock market has a knock on reputational effect upon the valuation of its biotechnology partner. The alliance offers uncertainty reduction information to shareholders about the likely success and value of Exploration and Development projects undertaken by the biotechnology firm, resulting in an increase in the value of the firm. The concluding chapter of this thesis highlights major implications that the findings of this study may have for both the pharmaceutical sector and industry in general.

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Chapter One:

Introduction

RESEARCH QUESTIONS

This thesis seeks to address three general research questions. Each of these questions is briefly outlined below. During the following discussion the reader is also informed of the chapter of this thesis that seeks to analyse each research question.

1. From a theoretical perspective, what is the knowledge Exploration/Exploitation dilemma?

This question consists of two sub questions:

- (a) From a theoretical perspective why should there be a tension between knowledge Exploration and Exploitation?
- (b) From a theoretical perspective why is it difficult to sustain efforts to increase knowledge stocks through Exploration or to appropriate a return from current knowledge stocks through Exploitation?

A number of scholars have argued in the literature that there is a tension between the Exploration for new organisational knowledge and the Exploitation, or development and use, of current stocks of organisational knowledge (Cohen and Levinthal, 1990; Kogut and Zander, 1992; Levinthal, 1997; and Levinthal and March, 1993). It has been argued that over time firms tend to invest increasing organisational resources to Exploitation activities at the expense of Exploration. It is argued that this occurs due to the shorter feedback loops that investments in Exploitation have relative to Exploration, which is by definition a highly uncertain and longer term activity, and the greater short term financial rewards that Exploitation activities attract (Levinthal and March, 1993). This bias towards Exploitation of current stocks of organisational knowledge is argued in the literature to pose a considerable long-term threat to the

prosperity and survival of a firm (Hendry, 1993; Levinthal, 1997; Levinthal and March, 1993; March, 1991). The threat to prosperity and survival occurs because investment in Exploitation to the detriment of Exploration implies that the ability of the firm to innovate and adapt is severely impaired, thus reducing its ability to respond to environmental shocks that require creation and implementation of new organisational capabilities (Leonard-Barton, 1995).

There exists a diverse literature on the challenges that promotion of both Exploration and Exploitation pose to firms and management. In addressing the above question Chapter Two reviews this literature to explore the principal problems that firms' face in both the maintenance of Exploration and Exploitation activities individually and the tension that exists between Exploration and Exploitation. Chapter Two condenses this review into a series of figures, cumulating in an overall framework mapping the tension within and between knowledge Exploration and Exploitation.

2. Is there evidence within a real organisational context that a firm's activities can be explained through the conceptual lens of balancing a tension between knowledge Exploration and Exploitation?

This question consists of three sub questions:

- (a) Can a firm's activities over time be categorised in terms of knowledge Exploration and Exploitation?
- (b) Does this analysis indicate that Exploration and Exploitation activities are in balance or not?
- (c) If a tension between balancing Exploration and Exploitation activities is found to exist then how does a firm's executive team manage this tension?

In addressing the above question three in-depth case studies of UK biotechnology firms, who are primarily in the business of discovery and development of drugs for human health, were conducted. Each case, as approved for publication by the management, is presented in Appendices One, Two and Three. The oldest of these three firms, Celltech, is the focus of analysis in Chapter Three. In this chapter Celltech

is analysed using the conceptual lens of Exploration/Exploitation and it is found that its core activities, namely the discovery and development of drugs and the management of inter-organisational collaborative partnerships, can be categorised as knowledge Exploration or Exploitation activities. This analysis does indicate that balance is not always maintained, however contrary to theory it is found that balance can be maintained over a period of five years. It is also found that the management of Celltech has sought to carefully manage both the tension between Exploration and Exploitation and the interface between these activities, through a combination of informal and formal monitoring and review systems.

3. Do the financial markets reward announcements of Exploitation activities with higher returns than Exploration activities, as predicted by theory?

In addressing this question announcements by UK biotechnology firms over a three-year period are classified as knowledge Exploration or Exploitation events. Using the event study methodology, which is outlined in some depth in Chapter Four, these events are analysed to determine whether shareholders reward positive announcements about Exploration and Exploitation by increasing the stock market valuation of the firm. Increases in share price over and above a number of performance hurdles, namely the contemporary performance of a market index or past average share price performance of the firm, are observed indicating that a tangible financial reward is ascribed to both Exploration and Exploitation. Such increases are referred to as abnormal returns.

Six value creation hypothesis are generated in Chapter Four, which are based on past conceptual and empirical studies in the literature in addition to evidence from the three in-depth case studies in the appendices. Past theoretical work (Levinthal and March, 1993) suggests that Exploitation activities should be accompanied by a greater financial reward than Exploration activities. The evidence from Chapter Four suggests that financial markets may attach a higher value to announcements of Exploitation activities than Exploration. Exploration events are found to be associated with abnormal returns of greater than 2%, while announcements of Exploitation events are

associated with abnormal returns of greater than 9%. It is also found that a key activity in the biotechnology sector, namely alliance formation (Powell, Koput and Smith-Doerr, 1996; Stuart, Hoang and Hybels, 1999), is associated with creation of additional shareholder wealth, generating abnormal returns of greater than 10%. Chapter Four argues that announcements of Prestige Alliances are rich in information about both the Exploration and Exploitation activities of biotechnology firms.

INDUSTRIAL CONTEXT

The empirical context of this thesis is a sample of UK biotechnology firms' the primarily focus of whom is the discovery and/or development of drugs to improve the treatment of human health, or the diagnosis of human diseases. Prior to detailing the selection of the sample and data collection procedures an overview of the pharmaceutical and biotechnology industry is provided. This is not meant as an exhaustive analysis of the sector, rather it seeks to provide readers who are not familiar with the industry a brief overview of its size and function. For a more detailed analysis of the sector the reader is referred to the excellent *Introductory Guide to Biotechnology* written by the Biotechnology Industry Association (BIO, 1999), the Ernst and Young Life Sciences Industry reports (Ernst and Young, 1999a, 1999b, 1998) and Bogner and Thomas's (1996) book on creating value in the pharmaceutical industry.

Biotechnology defined

Biotechnology is generally defined by the UK BioIndustry Association as "the use of biological processes to make useful products (including modified organisms, substances and devices" (BioIndustry Association, 1999). The US Biotechnology Industry Organisation note that "biotechnology is often defined as a combination of advances in our understanding of molecular and cellular biology, plant, animal and human genetics and how the human immune system fights disease" (BIO, 1999). The use of biotechnology in a crude sense is an ancient activity. For example the production of beers and wines is an application of biotechnology in the food sector, while the production of penicillin is a more modern example (BIO, 1999).

Modern biotechnology came to life with the discovery of DNA (deoxyribonucleic acid), which can be simply thought of as the blue print of life (BIO, 1999). Three advances made the manipulation of DNA, and hence modern biotechnology, a practical reality, namely hybridoma technology, discovered by Kohler and Milstein in 1975 at Cambridge (Faulkner, Senker, and Velho, 1995), Recombinant DNA (rDNA), discovered by Boyer and Cohen in 1973 at Stanford University (Faulkner, Senker, and Velho, 1995) and Protein Engineering (Oxender and Graddis, 1991).

Applications of biotechnology and regulation

Further advances in molecular biology have enabled firms to gain a much greater understanding of biological organisms and how they can be manipulated to improve human health, crop yields and environmental protection. The application of modern biotechnology spans four important sectors in the world economy, namely, discovery and development of therapeutic drugs to improve treatment of human diseases, diagnostics tools to identify human and animal diseases, agricultural biotechnology, which involves the genetic modification of plants and animals with the goal of improving yields and nutrition, and environmental protection, such as clean up of hazardous wastes (BIO, 1999; Ernst and Young, 1999a).

Because biotechnology involves production through the manipulation of biological organisms it is a heavily regulated sector. Products that have been produced using biotechnology cannot be marketed without regulatory approval. Regulation of therapeutic drugs is undertaken by the Food and Drug Administration (FDA) in the USA, and in the EU by the European Medical Evaluation Agency (EMA), in co-operation with national regulators. The FDA and National Departments of Food and Agriculture regulate agricultural products. Drugs produced using biotechnological processes are required to pass a long series of regulated clinical trials to ensure that the drug is both safe for human consumption and brings clear therapeutic benefits. As this thesis focuses on therapeutic and diagnostic biotechnology firms the agricultural and

environmental biotechnology sectors are not reviewed¹, however an overview of the pharmaceuticals sector is provided.

The drug discovery and development process is highly regulated, costly and success is uncertain. An overview of this process is provided in Table One². This table details the major stages of the process, the length of time and cost of each stage, and the probability of a drug that enters a given stage making it from that stage through to market launch. Table One also offers insights into the regulatory and financial success of drug compounds. The process of moving a drug from discovery to regulatory clinical trials is highly uncertain, with less than 5 in 5,000 to 10,000 compounds making it from discovery to clinical trials (Berry, 1996; PhARMA, 1999). The whole process from discovery of a promising compound to eventual regulatory approval to market the drug is lengthy. For drugs launched on the market between 1990 and 1996 the process on average took 15 years (PhARMA, 1999). Drawing upon a sample of drugs that entered clinical trials between 1980 to 1984 DiMasi (1995) found that only 18.3% of these drugs had gained regulatory approval, and estimated that only 23.5% were expected to eventually gain regulatory approval. By 1998 80 biotechnology drugs had been approved for sale by the FDA (BIO, 1999), with 14 new biotechnology drugs approved in 1998 by the EMEA (Ernst and Young, 1999a). It can be expected that the number of biotechnology drugs will grow rapidly over the coming years. There are over 2,200 biotechnology drugs in the development process, with over 300 products in the final stage clinical trials (Ernst and Young, 1999b).

INSERT TABLE ONE ABOUT HERE

Patents: the reward for high risks and costs of regulatory approval

An important value driver in the pharmaceuticals business is the monopoly rents that patent laws provide. The monopoly rights and profits that patents bestow on drugs are meant to act as a reward for the high risks and costs attached to gaining regulatory

¹ Readers interested in the agricultural and environmental services sectors are referred to BIO (1999) and Ernst and Young (1999a; 1999b).

² In this thesis tables and figures for each chapter are presented at the end of the that chapter.

approval. Patent protection in the US and Europe for drugs extends for approximately 20 years. It is estimated by the Pharmaceutical Research and Manufacturers of America trade association (PhARMA) that the average patent protection afforded to drugs after they have gained regulatory approval is 12 years. They do, however, cite some examples of drugs that have had as little as a half a year of exclusivity (PhARMA, 1999). The costs and risks that patent monopoly rights seek to compensate for are substantial. The cost of taking a drug from discovery through to regulatory marketing approval was estimated by the Boston Consulting Group to be \$500m, when the cost of researching failures and interest charges were taken into account (PhARMA, 1999). The Association of the British Pharmaceutical Industry (ABPI) estimates that only one in seven drugs that receive regulatory marketing approval go on to become commercially successful (ABPI, 1999a). Grabowski and Vernon (1994) observed from a sample of US drugs introduced in the early 1980s that the average Net Present Value in 1990 US dollars was \$22 million per drug, though it was found that this result was highly skewed with only the top 30% of drugs recouping R&D and other costs.

Once a drug's patent begins to expire then it is quickly subject to intense competition from imitators. Under the *Drug Price Competition and Patent Term Restoration Act 1984* in the US and similar laws in Europe once a drug goes off patent then other firms can very quickly legally produce a generic version of the drug. The effect of generic competition is considerable. PhARMA (1999) report that for drugs whose patent expired in 1991-1992 generic drug imitators captured 20% of the market immediately upon expiry of first mover patent protection. Generic drugs had captured 44% of the market within 6 months and 72% of the market within 18 months. World-wide generic drugs represented 18.5% of prescription units in 1984, rising to 46.5% by 1998 (PhARMA, 1999). By the late 1990s it is estimated that 55% of all NHS prescriptions in England and Wales were written for generic drugs (ABPI, 1999b). In 1997 two of Glaxo-Wellcome's drugs began to go off patent world-wide. The effects in terms of sales were quite pronounced. Sales of Zantac fell 45% from £ 1,375 million in 1997 to £757 million in 1998. Sales of Zovirax fell 30.5% from £ 580 million in 1998 to £ 403

million in 1998 (Glaxo-Wellcome Annual Report 1998). This decline in sales was attributed to competition from generic drugs.

The challenge that expiry of patents pose to pharmaceutical firms is often cited as one of their main strategic challenges. Pressure group *Generic Access* note that most generic drugs are priced at 25% or less than branded drugs and that over the next 12 years patents will expire on drugs with current sales of \$41 billion (Generic Access, 1999). This represents 13.4% of the current \$306.3 billion global drug market (IMS Health, 1999). Ernst and Young (1999a) note that about half of the sales of Eli Lilly and Merck are derived from drugs that will go off patent by 2003. The challenge for pharmaceutical firms who wish to maintain high net profit margins and sales growth is to replace these drugs with new patented drugs. To do so pharmaceutical firms invest about 20% of their turnover in R&D, making them the most R&D intensive private sector funded industry in the UK and US (ABPA, 1999a; PhARMA, 1999). The UK pharmaceutical sector invested £2.2 billion in R&D in 1997, while the US pharmaceutical firms invested \$20.6 billion (ABPA, 1999a; PhARMA, 1999).

It is expected that biotechnology will play an important role in pharmaceutical firms' search for new drugs. The PhARMA *Pharmaceutical Industry Profile 1999* notes that "Currently there are 500 distinct targets for drug interventions. That figure is expected to increase 6 – to 20 fold, to 3,000 to 10,000 drug targets in the near future." PhARMA argues that the key driver of this expansion is developments in biotechnology and genomes. It is noted by Ernst and Young (1999a) that an estimated 30% of pharmaceutical firms' R&D budgets are available for external alliances and that much of this money may be targeted at alliances with biotechnology firms. 30% of 1997 pharmaceutical budgets of UK and US firms would amount to about \$ 7 billion. In 1998 the largest 100 biotechnology alliances netted biotechnology firms revenues of \$1,786 million (Recombinant Capital, 1999). The top 20 pharmaceutical firms entered into 226 new alliances with biotechnology firms in 1998 alone (Van Brunt, 1999). In addition to financial payments to their biotechnology partners a substantial amount of their R&D budget would have been consumed on costs associated with the running clinical trials on drugs developed with biotechnology partners.

Biotechnology and the pharmaceutical sector

Table Two compares the size of the pharmaceutical sector with that of the biotechnology sub-sector. The world-wide pharmaceutical market is very large, with \$306,300 million in sales during 1998. The sector is relatively concentrated with the top ten drugs representing 8.2% of the total market, all of which had sales in excess of \$1,000 million. UK firms sold three of the top ten drugs. These three drugs generated combined sales of \$7,218 million³. The top ten pharmaceutical firms in terms of sales represented 29.6% of the world-wide market. Three of these companies were UK based, with combined sales of \$ 28.4 billion⁴. As a whole the UK pharmaceutical and biotechnology sector generated a trade surplus with the rest of the world of £2.6 billion (ABPI, 1999c).

INSERT TABLE TWO ABOUT HERE

In contrast to the top ten drugs by sales, the top ten biotechnology drugs in terms of sales represented 2.5% of the world-wide market, while the revenues of the US and European biotechnology sectors combined, totalling some 2,461 firms (see Table Four), have combined revenues that are only 5.3% the size of total sales in the pharmaceuticals market world-wide. Revenues from the 32 therapeutic biotechnology firms, which this thesis focuses upon, represents 0.1% of the global market in terms of revenues. From the revenue picture it could be argued that the biotechnology sector is of relatively little importance, however this would be misleading.

The value driving engine of the pharmaceutical business is R&D of novel patented drug compounds (Ernst and Young 1999a). Margins from patented drugs are higher than non-patented sales and it is expected that much of the future pipeline of patented

³ \$ 3,858 million sales of Losec by AstraZeneca, \$ 1,760 million sales of Seroxat by SmithKline Beecham, and \$ 1,169 million sales of Augmentin by Smithkline Beecham.

⁴ Glaxo-Wellcome with pharmaceutical sales of \$ 10.5 billion, SmithKline Beecham with sales of \$ 7.3 billion, and AstraZeneca with combined sales of Astra \$ 6.9 billion and Zeneca of \$ 3.7 billion (Firm, 1999).

drugs shall be derived from biotechnology. Table Three provides details of the revenue, R&D spend, net losses, and number of staff for firms in the European and US independent biotechnology sectors. It can be seen that while the entire European sector is smaller than Glaxo-Wellcome in terms of revenues, R&D spend per employee is considerably higher. As noted above pharmaceutical firms are amongst the most R&D intensive in the world in terms of percentage of turnover invested in R&D, yet the biotechnology sector is even more R&D intensive from the perspective of R&D per employee. European biotechnology companies spent £ 32,775 per employee on R&D compared to £ 20,415 per employee by Glaxo-Wellcome, the world's largest pharmaceutical firm in 1998 (see Table Three). The industry is very heavily in the red, with net losses in Europe amounting to £1,496 million and in the USA amounting to £3,071.5 million. These net losses reflect the level of investment in R&D of the sector and the fact that few have any significant revenues generated from product sales due to the lengthily period it takes to steer a drug through the regulatory approval process, combined with the relative youth of the sector⁵.

INSERT TABLE THREE ABOUT HERE

⁵ Genentech, the world's oldest therapeutic biotechnology firm, was founded in the USA by Robert Swanson, a venture capitalist, and Dr Herbert Boyer, one of the co-discoverers of Recombinant DNA (rDNA), in 1976. Genentech was listed on the NASDAQ stock exchange in 1980. This listing raised \$ 35 million for Genentech. In 1982 the first rDNA drug (human insulin), developed by Genentech and licensed to Eli Lilly, was launched on the market. In 1985 Genentech received marketing approval from the FDA for the first biotechnology drug, called Protopin, to be developed, manufactured and marketed by a biotechnology firm (Genentech, 1999). In January 2000 Genentech had a market capitalisation of \$ 34.4 billion.

Celltech, the oldest UK therapeutics biotechnology company, was founded in 1980. Celltech was listed on the London Stock Exchange in 1993. This listing raised £ 30 million for Celltech and was at the time the largest ever placing and public offer of shares of a biotechnology business in Europe. Its first drug, Chirocaine (originally developed by fellow UK biotechnology firm Chiroscience, which merged with Celltech in 1999), was approved for marketing in Europe in 1999. This drug was the first major drug discovered and developed through to marketing approval by a UK biotechnology firm. (Appendix One, the Celltech case study; Ernst and Young, 1999a). In January 2000 Celltech had a market capitalisation of £ 1,081 million.

From Table Four it can be seen that the number of biotechnology firms in both Europe and the US has grown over the last two years. While publicly quoted companies represent only 5.7% of European biotechnology firms in number (68 firms out of a total of 1,110) their combined R&D spend of £ 541 million, is 32.6% of the total R&D spend of the European biotechnology sector. The R&D spend of publicly quoted European firms is much higher than private firms £ 42,504 per employee for public companies versus £ 30,100 for private firms. The R&D spend per employee of UK public biotechnology firms is even more pronounced. The 32 therapeutic biotechnology firms studied in this thesis spend £ 67,100 on R&D per employee (see Table Eight).

INSERT TABLE FOUR ABOUT HERE

From Table Five it can be seen that three countries dominate the European biotechnology sector: 23% of European biotechnology firms are located in the UK, 19% are located in Germany and 12% are located in France. It should be noted that the 32 publicly quoted therapeutic and diagnostic firms that are the empirical focus of this thesis represent 47% of the number of European publicly quoted biotechnology firms, and greater than 20% of the total R&D expenditures of the wider European biotechnology sector (see Tables Three, Four and Eight).

INSERT TABLE FIVE ABOUT HERE

The European biotechnology sector in general, and the UK sector in particular, are many years away from significant revenues generated by sales of drugs. To date only one UK biotechnology company has had a drug approved for marketing, Chirocaine, by Celltech-Chiroscience. With a lack of profits from drug sales to fund R&D expenditures independent biotechnology firms in Europe and the UK are dependent on two primarily sources of cash: funds raised from shareholders' equity and revenues raised through collaborative agreements. From Table Six it can be seen that the amount raised from shareholders has declined in the US but risen in Europe. Combining the data from Table Three with that of Table Six it can be seen that public biotechnology firms in Europe raised £ 358.2 million, while incurring net losses of £ 291.1 million.

These companies need additional sources of funding if they are to not return to the market quickly. Some such funds are obtained via alliances.

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From Table Seven it can be seen that in 1998 European biotechnology firms entered into 146 strategic alliances. These alliances serve a number of purposes. The first is access to funds, second is access to drug development capabilities that the biotechnology firm may lack, third is access to marketing and distribution capabilities that they often also lack, and fourthly is the validation that these alliances bring to biotechnology firms in the eyes of their shareholders. Ernst and Young (1999a) excellently summarise a widely held view about the importance of alliances for biotechnology firms when they noted that:

“Alliances remain the lifeblood for ELISCOs {biotechnology companies}. The current reality in Europe is that achieving successful alliances is one of the most important validations of an ELISCOs commercial potential. In time successful in-house product development may become an achievable goal, but for the present the realistic model for Europe is one that focuses on solid research with clinical development. ... The relative importance of strategic alliances, however, reflects the simple truth that collaborators are closer to the market and are therefore better able to assess the commercial potential of ELISCO products and technologies. This importance grew in 1998 as capital funding generated through alliances was one of the more important sources of funding for ELISCOs”

INSERT TABLE SEVEN ABOUT HERE

Table Seven offers an insight into the financial potential of alliances for biotechnology firms. Collaborators typically undertake much of the cost of development of a biotechnology firm's drug; in addition they provide a valuable source of cash. Revenues earned by the top 100 biotechnology alliances for biotechnology firms amounted to \$1,786 million in 1998, an increase of 24.5% over the prior year (Recombinant Capital, 1999).

Table Eight provides detailed information on the financial performance of the principal 32 publicly quoted UK therapeutic and diagnostic biotechnology firms in 1997 and 1998. It can be seen that as a group they invested 127% of their turnover on R&D, leading to a combined net loss of £ 296.6 million in 1998. They are very R&D intensive firms, investing £ 67,190 per employee in 1998 compared to £ 20,415 by the UK's largest pharmaceutical firm, Glaxo-Wellcome and £ 42,504 for publicly quoted European Biotechnology firms as a group (see Table Three). Bearing in mind that only one of these firms, Celltech-Chiroscience, has taken a drug from discovery all the way through to regulatory approval for marketing they remain, as a group, a considerable number of years away from break-even based on product sales, or alliance revenues (Ernst and Young 1999a). Cash Burn is therefore critical to these firms. Cash burn is calculated as the current cash and equivalents of the firm divided by net losses. The figure gives an insight into how long the firm could continue to incur the current rate of losses without returning to the capital markets for additional equity or go bankrupt. As can be seen from Table Eight the average for these 32 firms is 2.37 years, a period considerably shorter than commentators' estimate it will take for these firms to break-even based on product sales. Thus a critical competitive aspect for these firms is their ability to communicate to shareholders that their investment is valuable (and by implication worth shareholders reinvesting in via follow-on equity offerings) and their ability to form revenue generating and cost sharing alliances, both of which conserve cash. Both of these issues received attention in this thesis.

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SAMPLE SELECTION

UK biotechnology and the tension between Exploration and Exploitation activities

The reason why this thesis focuses on the UK biotechnology sector for its empirical study is that this sector should be an extreme example of the challenges of knowledge Exploration and Exploitation. As argued above, the value creating engine of this sector is the process of drug discovery and development to create and replenish portfolios of patented drugs. Discovery of new drugs can be viewed as essentially being a

knowledge Exploration activity, involving the search for new knowledge on the treatment of a disease and embedding that knowledge in a patented drug compound. The rewards from such Exploration are considerable. From Table Three it can be seen that Glaxo-Wellcome, while investing over a billion pounds per year in the R&D of new drugs, it earned a net profit margin of 33% in 1997 and 1998. The motivation for UK biotechnology firms to invest in Exploration for new drugs is strong, and reflected in a combined market capitalisation of £3,9474.5 million in 1998, despite net losses of £ 296.6 million (see Table Eight).

The pull of Exploitation is also very strong in the biotechnology sector. From Table Eight it can be seen that the cash burn for the sector, as a whole, is 2.37 years. This varies from a low of 0.52 years for Tab to a high of 12.97 for Celltech. The pressure that low cash burns bring is tangible. Despite being the first biotechnology firm to have a drug approved for marketing difficulties in retaining AstraZeneca as a marketing partner exposed Chiroscience to considerable uncertainties. With a cash burn of only 1.15 years Chiroscience was exposed to intense financial pressures and was taken over by Celltech, who has both a strong relationship with its shareholders and a cash burn of 12.97 years. Tab had a potentially exciting anti snake bite venom about to be approved in 1999, however with a cash burn of 0.52 years it too succumbed to take-over, this time by Proteus International, who also has a low cash burn ratio. Efforts to balance the tension between Exploration for innovative compounds, which consumes large amounts of cash (as much as \$ 500 million per drug if cost of failures is factored into the equation, PhARMA, 1999), and Exploitation of current stocks of knowledge through alliances and follow-on equity offerings are likely to be intense. For these reasons it was thought that this sector would offer a potentially rich source of field data in the study of the tension between Exploration and Exploitation.

Selection of sample companies

Three biotechnology firms were selected for in-depth case studies. The purpose of these case studies was twofold. First, to gain a familiarity with the UK biotechnology

sector. Second, to study the management of organisational knowledge within these firms, to gain an insight into whether or not a tension between Exploration and Exploitation activities exists within an industry where it is expected to occur, and to see how this tension is managed if found to be present. The three cases were selected on two criteria. The first was to gain a temporal spread of the sector. The second was to gain a technological and competitive spread. From a temporal perspective Celltech was chosen because it was the oldest biotechnology firm in the sector, having been formed in 1980 and floated on the London Stock Exchange in 1993. Oxford Molecular was chosen as a representative of the middle aged firms, having been founded in 1989 and floated on the London Stock Exchange in 1995. PolyMASC was chosen to represent the newer firms in the sector. It was founded in 1995 and immediately floated on the Alternative Investment Market.

From a competitive and technological perspective these cases were chosen as they offered an interesting overview of the sector. Celltech is a drug discovery and development company. Its goal is to discovery novel compounds and, through alliances with major pharmaceutical firms, to take these drugs through regulatory development clinical trials and onto the market. The ultimate return for Celltech is a share of royalties from drugs that it discovered that eventually gain regulatory marketing approval. Oxford Molecular does not seek to independently discover or develop drugs, rather it manages networks of university and commercial partners to discovery new compounds. The ultimate return for Oxford Molecular is a management fee that it obtains from pharmaceutical or biotechnology firms for whom it manages the drug discovery process. Essentially Oxford Molecular is a contract services firm. PolyMASC is a drug delivery company. It discovers novel drug delivery mechanisms that can be applied to drugs to facilitate easier use by the patient (e.g. to take a drug in oral, pill, form rather than as an injection) and/or improve the clinical effectiveness of the drug. The ultimate return for PolyMASC is a share of the royalties from drugs that apply its delivery mechanism. Thus these three cases span the industry from drug discovery and development (Celltech), to service support (Oxford Molecular), to complementary products (PolyMASC).

Each case study was created with the co-operation of the management; thus all cases have received clearance from the firms for publication. All interviews with managers inside the firms were transcribed and a chain of evidence carefully maintained (Yin, 1989). Respondent validation was sought through a series of iterative re-writes where the researcher's interpretation of the events in the company were checked with managers inside the firm (Silverman, 1993), culminating in the case studies presented in the appendices. Collection of additional data from company documents and financial media sources (via the Reuters Business Briefings database) augmented data from interviews. The focus of each case was upon specific drug discovery and development projects and alliances. Through such practical activities the Exploration and Exploitation of knowledge could be tangibly observed. Details of the case methodology are provided in the analysis of the Celltech case in Chapter Three.

Selection of the 32 UK biotechnology firms to be included in the event study involved the creation of a sampling frame of all UK therapeutic and diagnostic biotechnology firms quoted on the London Stock Exchange up to the end of 1998. A company was included in the sample if two of the following three sources listed it as a therapeutic or diagnostic biotechnology firm: the Ernst and Young *European Life Sciences Report 1999* or *1998*, *Pharmaceutical Business News*⁶, or *Genetic Engineering News Directory of Biotechnology 1999*⁷. Each of these three publications are well regarded as important sources of information about the European and UK biotechnology sectors. Review of these three sources resulted in the creation of a list of 32 companies as outlined in Table Seven. Further information on quoted UK biotechnology stocks was sought through discussions with the case study interviewees, two interviews conducted with managers in the London Stock Exchange, and a search of UK financial media and newswire services using the *Reuters Business Briefings* database.

⁶ *Pharmaceutical Business News* is published every two weeks by the *Financial Times* (London). During 1998 and 1999 the publication was split into a number of sections, one of which was called Bio-Europe, offering information on the activities of European biotechnology firms

⁷ The *Genetic Engineering News Directory of Biotechnology Companies* is published annually by *Genetic Engineering News* (Larchmont, New York), which claims to be the oldest biotechnology trade magazine in the world.

STRUCTURE OF THESIS

The thesis is structured into five chapters, including this introduction, and five appendices. **Chapter Two** reviews the literature on the management of the tension between knowledge Exploration and Exploitation. The literature is interpreted via a series of figures that seek to illustrate the tension within and between the processes of knowledge Exploration and Exploitation. **Chapter Three** analyses the Celltech case study using the conceptual lens of Exploration and Exploitation. This case was found to be the most illustrative of the tension between Exploration and Exploitation and the management thereof over a period of a decade. **Chapter Four** undertakes an event study of all announcements of completion of pre-clinical trials (drug discovery), phase I, II and III regulatory clinical trials, and announcements of the formation of alliances. These announcements are interpreted in the context of six hypotheses. **Chapter Five** seeks to summarise and draw the findings of Chapters Two, Three and Four into a set of overarching conclusions. Appendix One details the Celltech case study. Appendix Two provides the PolyMASC case. Appendix Three provides the Oxford Molecular case. Appendix Four, in keeping with the event study methodology, lists all events included and excluded from the sample. Appendix Five lists all conference papers and publications completed during registration as a doctoral student at City University.

TABLE ONE: THE DRUG DISCOVERY AND DEVELOPMENT PROCESS

Stage	Pre-Clinical	Phase I	Phase II	Phase III	Regulatory Approval and Market Launch	PIV Testing
Purpose	Synthesis and screening of compounds Toxicology safety and dosage testing Involves pre-clinical trials using animals	Establish safety in human volunteers	Establish safety and efficacy in human patients	Establish efficacy relative to other therapies on the market	Submit results of clinical trials to gain regulatory approval Process development, distribution and marketing	On-going monitoring of drug in market to ensure safety and efficacy
Time¹ (15 years in total)	6 years	27% of time	6.7 years 27% of time	46% of time	2.2 years	on-going
Cost² (\$300 to \$500 million in total)	40.6%	11% of cost	26.5% 27% of cost	62% of cost	27%	5.8%
Number of Compounds entering stage³	5 to 10,000 screened 250 enter pre-clinical trials	5 compounds enter clinical trials				
Probability of compound making it to market⁴	3-5%	10%	30%	60%	90%	N/A
Regulatory Success	Only 23.5% of drugs that entered clinical trials between 1980 and 1984 were expected to gain regulatory approval to be marketed (DiMasi 1995)					
Financial Success:	The Net Present Value of drugs introduced onto the US market between 1980 to 1984 was \$ 22 million in 1990 dollars. Only 30% of drugs launched on the market generated enough revenues to recoup R&D and other associated costs (Grabowski and Vernon 1994)					

¹ Average number of years obtained from PhARMA (1999) annual survey of the US pharmaceuticals sector

² Percentage of time for Phase I, II and III trials from Pharmaceutical Education and Research Institute, 1996

³ Percentage total costs from PhARMA, 1999 annual survey of US pharmaceuticals sector

⁴ Percentage of cost attributable to Phase I, II and III clinical trials from Pharmaceutical Education and Research Institute, 1996

⁵ Source PhARMA, 1999

⁶ Source Zeneca/Lehman Brothers, as quoted in Brown and Srinathan, 1999.

TABLE TWO: SIZE OF THE PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRY IN 1998⁸

	Revenue 1998 \$ million	Percentage of Global Pharmaceutical Sales
World-wide Pharmaceutical Sales	306,300	100.0
Sales of Top 10 Drugs ⁹	25,025	8.2
Sales of Top 10 Biotech Drugs (1997) ¹⁰	7,546	2.5
Pharmaceutical Sales of Top 10 Drug Companies	90,700	29.6
US Biotechnology Sector Revenues	13,218	4.3
European Biotechnology Sector Revenues	3,107	1.0
Revenues of 32 Quoted UK Therapeutic Biotechnology Firms ¹¹	349	0.1
Glaxo-Wellcome Sales	10,500	3.4

Sources: Company Annual Reports, Ernst and Young 1999a; 1999b; Hemscott.com; IMS Health 1999.

⁸ Unless specifically stated all data in the following tables on the biotechnology sector includes firms engaged in therapeutics, diagnostics, agri-biotechnology, and environmental sciences. Ernst and Young (1999a) indicate that about 90% of the European sector is focused upon therapeutics and diagnostics.

⁹ Top ten therapeutic drugs by worldwide sales are: Losec (\$3,858m, AstraZeneca), Zocor (\$3,600m, Merck and Co, 1997 sales), Prozac (\$2,811.5, Eli Lilly), Norvasc (\$2,575m, Pfizer), Liptor (\$2,185m, Warner Lambert Pfizer), Vasotec (\$2,500m, Merck and Co, 1997 sales), Seroxat (\$1,760m, SmithKline Beecham), Zolofit (\$1,836m, Pfizer), Augmentin (\$1,600m, SmithKline Beecham), Clartin (\$2,300m, Schering Plough). Source IMS (1999) and Company Annual Reports.

¹ Sales data for top ten biotechnology drugs in 1998 was not available, thus 1997 figures are quoted. World-wide sales are as follows: Procrit (\$1,169m, Amgen/Ortho Biotech), Epogen (\$1,161m, Amgen), Neupogen (\$1,056m, Amgen), Epivir (\$973m, BioChem Pharma Glaxo Wellcome), Humulin (\$936m, Genentech/Eli Lilly), Intron (\$598m, Biogen Schering Plough), Enderix B (\$584m Genentech SmithKline Beecham), Bataseron (\$387m, Chiron Berlex Schering AG), Genotropin (\$349m, Genentech/Pharmacia and Upjohn), Ceredase (\$333m, Genzyme) Source Ernst and Young (1999b).

¹¹ All 32 firms are listed in table seven, where details of their revenues, net losses, R&D expenditure, cash balances, number of employees and market capitalisation is provided. These 32 firms represent 47% of the publicly quoted biotechnology firms in Europe and 20% of total biotechnology R&D spend.

TABLE THREE: THE SIZE OF GLOBAL BIOTECH EUROPEAN AND USA BIOTECHNOLOGY SECTORS COMPARED TO GLAXO

WELLCOME¹²

	1998 Revenue (£ m)	1998 R&D (£ m)	1998 R&D as % Revenue	1998 Net Profit (Loss) (£ m)	1998 Net Profit (Loss) as % Revenue	1998 R&D spend per Staff	1997 Revenue (£ m)	1997 R&D (£ m)	1997 R&D as % Revenue	1997 Net Profit (Loss) (£ m)	1997 Net Profit (Loss) as % Revenue	1997 Number of Staff	1997 R&D spend per Staff (£)
EUROPEAN													
Public co	732.7	541.0	73.8	(291.1)	(39.7)	47,253	434.2	357.8	82.4	(232.5)	(53.5)	8,418	42,504
Private co.	1,900.7	1,116.1	58.7	(1,204.9)	(63.4)	32,693	1,391.6	921.9	66.2	(921.9)	(66.2)	30,627	30,100
Total	2,633.4	1,657.1	62.9	(1,496.0)	(56.8)	36,163	1,825.8	1,279.7	70.1	(1,353.4)	(63.1)	39,045	32,775
USA													
Public Co	9,154.0	3,733.9	40.7	(1,625.9)	(17.7)	35,225	7,161.0	2,898.4	40.5	(852.2)	(11.9)	94,000	30,834
Private	2,047.6	2,228.7	108.0	(1,445.6)	(70.6)	47,419	1,989.2	1,932.3	97.1	(1,080.0)	(54.3)	46,000	42,006
Co.	11,201.6	5,962.6	53.2	(3,071.5)	(27.4)	38,971	9,150.2	4,830.7	52.8	(4,830.7)	(52.8)	140,000	34,505
Total													
Glaxo-Wellcome	7,983.2	1,163.0	14.6	2,671.0	33.5%	21,398	7,530.1	1,083.4	14.4%	2,531.9	33.6%	53,068	20,415

Sources of data: Ernst and Young, 1999a; 1999b; Ernst and Young, 1998.

¹² In 1998 Glaxo-Wellcome was ranked joint largest pharmaceutical firm in the world by the IMS Health, World Review 1999, with a 3.4% world market share (Firm, 1999)

TABLE FOUR: NUMBER OF BIOTECHNOLOGY FIRMS: EUROPE VERSUS USA

	1998			1997		
	EUR	USA	Total	EUR	USA	Total
Public Companies	68	327	395	61	317	378
Private Companies	1,110	956	2,066	975	957	1,932
Total	1,178	1,283	2,461	1,036	1,274	2,310

Source of data: Ernst and Young, 1999a.

TABLE FIVE: NUMBER OF EUROPEAN BIOTECHNOLOGY FIRMS BY COUNTRY

	1998	1998	% Change in number	1997	1997
	Number	% of total		Number	% of total
UK	268	23.7	+7.2	250	24.1
Germany	223	18.8	+26.7	176	17.1
France	141	11.8	+5.2	134	12.9
Sweden	94	7.8	+13.3	83	8.0
Switzerland	68	5.6	+47.8	46	4.4
Netherlands	64	5.3	+0.0	64	6.2
Belgium	55	4.6	+19.6	46	4.4
Denmark	50	4.2	+6.4	47	4.5
Finland	49	4.1	+2.1	48	4.6
Italy	43	3.6	+2.4	42	4.1
Ireland	36	3.1	+0.0	36	3.5
Others	87	7.4	-54.7	64	6.2
Total	1,178		+10.8%	1,036	

Source of data: Ernst and Young, 1999a; Ernst and Young, 1998.

TABLE SIX: EQUITY RAISED BY BIOTECHNOLOGY FIRMS: EUROPE VERSUS USA

	1998 (£ million)			1997 (£ million)		
	EUR	USA	Total	EUR	USA	Total
Initial Public Offerings	170.3	397.0	567.3	127.8	1,072.6	1,200.4
Venture Capital	126.0	465.1	591.1	109.5	435.2	544.7
Follow-on offerings	187.9	661.0	848.9	100.5	2,093.1	2,193.6
	484.2	1,523.1	2,007.3	337.8	3,600.9	3,938.7

Sources of Data: Ernst and Young, 1999a; 1999b; 1998.

TABLE SEVEN: BIOTECHNOLOGY FIRMS ALLIANCE ACTIVITY

	1998	% change	1997
Number of Strategic Alliances by European Biotech Firms	146	-14.1%	170
Top 20 Pharmaceutical firms Number biotech alliance partners	226	NA	NA
Revenue earned by Top 100 Biotech firms from alliance partners	\$1,786 m	+24.5%	\$1,434 m

Sources of data: Ernst and Young 1999a; 1998; Recombinant Capital, 1999.

TABLE EIGHT: PERFORMANCE OF UK QUOTED THERAPEUTICS BIOTECHNOLOGY FIRMS

Company	Turnover ¹¹ £'000		Net Profit £'000		R&D £'000		Cash £'000		Staff		R&D per Employee		Cash Burn ¹⁴ (Cash/Loss) 1998 1997		Market Cap. £ million 1998 1997	
	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997
Alzyme	0	0	(4,661)	(3,387)	4,025	2,694	3,723	2,588	8	9	503,130	299,330	0.80	0.76	10.5	5.8
Biocompatibles	16,209	14,554	(45,674)	(29,480)	14,934	12,530	24,741	46,976	486	496	30,730	25,260	0.54	1.59	583.8	447.8
Biotech	10,441	6,980	1,247	550	1,055	822	527	500	80	76	13,190	10,820	NA	0.91	32.4	26.2
British Biotech	454	10,100	(44,839)	(28,500)	42,244	36,277	132,762	183,300	445	380	94,930	95,470	2.96	6.43	241.7	814.1
Cambridge Antibody	1,134	1,354	(6,951)	(8,355)	9,125	6,693	34,824	44,182	119	66	76,680	101,410	5.01	5.29	54.9	78.4
Cantab	3,933	7,653	(9,852)	(6,030)	12,099	12,310	31,211	41,756	124	108	97,570	113,980	3.17	6.92	86.5	118.4
Celltech ¹⁵	11,700	4,300	(3,100)	(12,000)	21,500	18,200	40,200	36,300	208	202	103,370	90,100	12.97	3.03	319.5	202.5
Celsis	14,552	11,123	(934)	(5,587)	2,252	2,798	3,628	5,427	272	240	8,280	11,660	3.88	0.97	26.1	90.1
Chiroscience	26,200	11,500	(23,300)	(19,300)	36,400	18,800	26,700	51,400	302	212	120,530	88,680	1.15	2.66	328.9	275.7
Core Group	16	0	(5,898)	(4,688)	4,418	3,638	15,200	22,900	83	59	53,230	61,660	2.58	4.88	11.5	49.0
Cortecs	7,900	7,700	(19,800)	(14,500)	16,700	15,000	35,300	44,800	309	256	54,050	58,590	1.78	3.09	18.0	118.3
K S Biomedix	0	0	(1,020)	(847)	539	520	8,577	2,901	13	9	41,460	57,780	8.41	3.43	104.3	45.1
Oxford Asymmetry ¹⁶	14,900	10,100	3,710	2,040	980	466	14,700	30	187	117	5,240	3,980	NA	NA	211.5	0.0
Oxford Bio Medica	50	3	(3,681)	(2,925)	2,982	1,972	3,566	1,512	31	16	96,190	123,250	0.97	0.52	11.0	14.5
Oxford Glyco Sciences	5,110	1,923	(8,700)	(7,636)	8,700	7,600	40,100	11,090	113	74	76,990	102,700	4.61	1.45	78.5	0.0
Oxford Molecular ¹⁷	18,301	15,641	(1,228)	256	6,622	4,942	7,283	19,567	248	170	26,700	29,070	5.93	NA	48.1	141.7

¹³ Includes revenues from milestone payments by alliance partners, product and service sales.

¹⁴ Cash burn represents the number of years a firm could continue to sustain its current level of net losses without returning to the market for capital. Cash burn is a critical measure in the biotechnology sector as most firms are many years away from achieving breakeven because of the decade or more that it takes to steer a drug through the regulatory approval process.

¹⁵ Celltech case study is available in Appendix One. Celltech merged with Chiroscience in 1999. The merged company became known as Celltech-Chiroscience. In November 1999 Celltech-Chiroscience announced its intention to merge with Medeva. The new company shall be re-named the Celltech Group.

¹⁶ Oxford Asymmetry listed on the London Stock Exchange in March 1998.

Company	Turnover £'000 1998 1997	Net Profit £'000 1998 1997	R&D £'000 1998 1997	Cash £'000 1998 1997	Staff 1998 1997	R&D per Employee 1998 1997	Cash Burn (Cash/Loss) 1998 1997	Market Cap. £ million 1998 1997
Peptide Therapeutics	731 3,234	(7,513) (6,454)	8,107 9,745	9,754 20,751	83 61	97,670 159,750	1.30 3.22	37.7 97.7
Phytopharm	713 45	(3,634) (3,552)	3,863 2,930	2,455 6,450	31 26	124,610 112,690	0.68 1.82	49.5 19.6
PolyMASC ¹⁸	583 528	(1,586) (975)	851 ¹⁹ 661	1,373 1,956	13 13	65,460 50,850	0.87 2.01	14.2 27.0
Powderject	3,122 500	(4,708) (3,100)	7,309 2,500	18,992 5,040	124 58	58,940 43,100	4.03 1.63	340.1 112.6
PPL								
Therapeutics	478 1,140	(14,245) (10,209)	13,523 10,956	25,835 21,348	209 163	64,700 67,210	1.81 2.09	52.7 56.9
Proteome Sciences	0 0	(1,851) (1,497)	905 760	1,450 3,000	8 6	113,130 126,670	0.78 2.00	11.5 29.1
Proteus International ²⁰	178 573	(4,127) (3,824)	4,526 4,682	3,327 6,937	83 59	54,530 79,360	0.81 1.81	26.7 21.4
Quadrant Healthcare	1,261 2,011	(5,305) (2,898)	4,879 2,573	25,179 6,326	61 36	79,980 71,470	4.75 2.18	39.1 0.0
Scotia Holdings	18,600 18,900	(18,600) (20,700)	22,900 23,000	52,700 18,200	346 416	66,180 55,290	2.83 0.88	68.2 316.9
Shield								
Diagnostics ²¹	7,425 5,753	463 (1,331)	1,096 1,288	1,948 1,160	108 99	10,150 13,010	NA 0.87	103.1 140.3
Shire	80,328 41,798	6,247 421	28,985 17,884	29,665 10,283	417 253	69,510 70,690	NA NA	587.5 337.2
SkyePharma	10,925 13,839	(16,428) (11,948)	5,712 6,109	30,900 8,700	279 280	20,470 21,820	1.88 0.73	328.3 185.6
Stanford Rook	210 0	(1,580) (1,760)	NA NA	3,660 NA	NA NA	NA NA	2.32 NA	26.5 16.9
Tab	700 400	(15,900) (16,800)	11,400 11,500	8,200 6,900	NA NA	NA NA	0.52 0.41	11.3 49.2
Tepnel Life Sciences	135 270	(2,587) (1,530)	1,936 2,068	5,144 8,050	42 28	46,100 73,860	1.99 5.26	9.1 29.5

¹⁷ Oxford Molecular case study is available in Appendix Three.

¹⁸ PolyMASC was taken over by Valentis, a NASDAQ listed US drug delivery company, in 1999, name changed to Valentis. The PolyMASC case study is available in Appendix Two.

¹⁹ R&D is not separated in the PolyMASC Profit and Loss Account, thus operating costs are quoted here.

²⁰ Proteus International took over Tab in 1999, company renamed Protherics.

²¹ Name changed to Axis-Shield in 1999 following the takeover of Axis Biochemicals ASA in 1999.

Company	Turnover £'000		Net Profit £'000		R&D £'000		Cash £'000		Staff		R&D per Employee		Cash Burn (Cash/Loss)		Market Cap. £ million	
	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997	1998	1997
Vanguard	4,576	1,551	(15,972)	(21,158)	21,059	22,399	48,292	59,347	54	38	389,980	589,450	3 02	2.80	65.5	114.7
Medica	4,865	1,092	(14,636)	(14,803)	16,383	12,976	11,392	15,161	145	126	112,990	102,980	0.78	1.02	9.4	41.0
Xenova	265,730	194,115	(296,643)	(263,607)	338,009	277,293	703,308	714,838	5,031	4,152	67,190	66,790	2 37	2.71	3,947.5	4,023.2
Total																

Sources of Data: Company Annual Reports and web-sites, Datastream International database, Extel database, and Hemscott (1999).

Chapter Two

The Antagonistic Nature of Knowledge Management:

The Balance between Knowledge Exploration and Exploitation

INTRODUCTION

In the last decade there has emerged a group of scholars who argue that the central value adding task of the firm is the creation, storage and application of knowledge (for example: Grant, 1996a and b; Huber, 1991; Kogut and Zander, 1992; Leonard-Barton, 1995; Liebeskind, 1996; Mahoney, 1995; March, 1991; Nonaka and Takeuchi, 1995; Pisano, 1994; Teece, 1998). Their perspective is often referred to as the Knowledge Based View of the Firm²². It is an outgrowth of five rich literature streams, namely, Epistemology, Organisation Learning, the Resource Based View of the Firm, Organisational Capabilities and Innovation and New Product Development (Grant and Baden-Fuller, 1995).

In this chapter organisational knowledge is viewed as being embedded in a firm's administrative routines, capabilities, and product/service offerings²³. This chapter takes

²²Grant and Baden-Fuller (1995) note that the Knowledge Based View of the Firm is "an emerging theory of the existence, organisation and competitive advantage of the firm which {is} based upon the role of firms in creating, storing and applying knowledge."

²³ Grant (1996a) defines *routines*, noting that "the essence of an organisational routine is that individuals develop sequential patterns of interaction which permit the integration of their specialised knowledge without the need for communicating that knowledge ... this co-ordination relies heavily upon procedures in the form of commonly understood roles and interactions established through training and constant repetition, supported by a series of explicit and implicit signals "

Capabilities can be defined as "information based, tangible or intangible processes that are firm specific and are developed over time through complex interactions among firm's resources ..

the perspective of the firm as a knowledge creation and application system and as such falls within the domain of the Knowledge Based View of the Firm. A core issue that has been raised in this literature is the tension between Exploration for new organisational knowledge and the Exploitation of current organisational knowledge. This tension, often referred to as the Exploration/Exploitation dilemma, has become the focus of considerable theoretical and empirical research (for example: Cohen and Levinthal, 1990; Kogut and Zander, 1992; Levinthal, 1997; and Levinthal and March, 1993). One of the most influential works in this area is March's (1991) *Organisation Science* article "Exploration and Exploitation in Organisational Learning."

Within the existing literature, Exploration can be defined as "the pursuit of new knowledge of things that might come to be known" and Exploitation as "the use and development of things already known" (Levinthal and March, 1993). It is widely argued in the literature that a central component of success is the maintenance of a balance of Exploration and Exploitation within the firm (Cohen and Levinthal, 1990; Levinthal, 1997; Levinthal and March, 1993; Hendry, 1996). March (1991) sums up the sentiments within the literature when he observed that the maintenance of a balance between Exploration and Exploitation is "a primary factor in system survival and prosperity."

It should be noted at this point that the above definition of Exploitation, by Levinthal and March, incorporates both knowledge development and knowledge use. It is argued in this chapter that the distinction between knowledge development and knowledge use are important, though such a distinction is rarely explored in the literature. It is also argue in this thesis that an important linkage between Exploration and Exploitation, and hence long term survival, is knowledge development. Thus this chapter devotes considerable attention to a literature review of the concept of knowledge development.

unlike resources, capabilities are based on developing, carrying and exchanging information through the firm's human capital." (Amit and Schoemaker 1993).

Were balance a simple task then there would be no dilemma. Levinthal and March (1993) note that “although there are clear occasions on which organisations need to stimulate Exploitation and restrain Exploration, the more common situation is one in which Exploitation tends to drive out Exploration.” They argue that this is because “Exploitation generates clearer, earlier and closer feedback than Exploration. It corrects itself sooner and yields more positive returns in the near term. As a result, the primary challenge to sustaining an optimal mix of Exploration and Exploitation is the tendency of rapid learners and successful organisations to reduce the resources allocated to Exploration” (Levinthal and March, 1993).

This bias towards Exploitation is particularly problematic in fast moving environments where current administrative routines, capabilities, products and/or services can quickly become obsolete. While internal development may generate the new organisational knowledge needed to replace obsolete knowledge this may be both expensive and not always possible. In an increasingly interconnected economy firms cannot bear the burden of sole independent discovery and development of knowledge across all domains necessary to remain competitive. To do so is to become a victim of the Not-Invented-Here syndrome²⁴. Thus a key element of long-term survival is the process of Exploration of the external *and* internal organisational environment in the generation of new organisational knowledge. Exploration activities also need to be carefully managed with the goal of linkage to Exploitation and financial rewards.

In addressing the Exploration/Exploitation dilemma it is argued that previous authors have under emphasised two crucial points. First, the Exploration/Exploitation dilemma is more fully characterised not as a dyadic relationship, but rather as a triadic one. That is *Exploration for new stocks of organisational knowledge*, the *development of current stocks* of knowledge into forms amenable to appropriation, and the *use of current stocks of knowledge for appropriation* of a financial return. Thus the concept of Exploitation is explicitly divided into two related, but distinct, processes referred to as

²⁴ For an overview of the Not-Invented-Here syndrome the reader is referred to Leonard-Barton (1995), Chapter Six.

Development and Use for Appropriation. Second, this triadic relationship takes place in a wider system where there are the three protagonist²⁵ meta-processes (namely, Exploration, Development and Use for Appropriation), which promote the creation (Exploration), development, and application (use) of organisational knowledge and three accompanying antagonistic meta-processes, which are in conflict with each of these protagonists. These antagonistic processes are explained in depth later in this chapter. They are labelled Core Rigidities, Slow Rate of Learning and Imitation. An organisational process can be viewed as a routine which co-ordinates and integrates a number of organisational resources and capabilities to perform specific tasks. These routines can take many forms from simple rules, such as procedures for ordering office supplies, to complex cultural norms that guide social interaction, such as the norms of behaviour that guide the interaction of staff within and across university departments when deciding how to run an MBA course. When considering the role of routines in a firm one can loosely bind them into categories of routines that seek to achieve a common task. The bundling of these routines together could be referred to as meta-processes.

Contribution of this chapter

This chapter seeks to address the first research question asked in Chapter One, namely, *from a theoretical perspective, what is the knowledge Exploration/Exploitation dilemma?* To achieve this goal this chapter seeks to make three contributions. First, it acts as a literature review, providing an overview of past research on the knowledge Exploration/Exploitation dilemma. This literature review offers insights into why there exists a tension between knowledge Exploration and Exploitation. In so doing this chapter addresses the challenge posed by question one (a) in the introductory chapter, namely *from a theoretical perspective why should there be a tension between knowledge Exploration and Exploitation?* The discussion of this question is found

Protagonist is defined by the Little Oxford Dictionary (1986) as “chief person in a drama or story etc.” In this chapter the word protagonist is taken as meaning the chief, or most important, positive meta-processes in the management of a firm’s organisational knowledge. In this context the antagonistic processes are the principal processes that are in conflict with the protagonists.

primarily in two sections of this chapter: Exploration/Exploitation as a Triad and the Conclusions section.

Second, through a detailed discussion of each of the three processes, Exploration, Development and Use for Appropriation, part (b) of the first research question in Chapter One is addressed, namely, *from a theoretical perspective why is it difficult to sustain efforts to increase knowledge stocks through Exploration or to appropriation return from current knowledge stocks through Exploitation?* The discussion of this question is found primarily in two sections of this chapter: Antagonistic Processes and Some Pivotal Characteristics in the Antagonistic Nature of Knowledge Management. The first of these sections explains why it is difficult for a firm to sustain its individual efforts in Exploration, Development and Use for Appropriation. It is argued that this is due to the presence of three parallel antagonistic processes (namely Core Rigidities, Slow Rate of Learning and Imitation), which challenge the firm's ability to create new stocks of organisational knowledge through Exploration or to exploit current stocks of knowledge through Development and use. The second section offers some insights into how Exploration, Development and Use for Appropriation can be re-energised and their accompanying antagonists suppressed.

The third contribution of this chapter is to highlight that it is important to proactively manage all elements of the dilemma, Exploration, Development and Use for Appropriation. It is suggested that maximal value can be obtained where linkages across these three processes are managed. Rather than focusing individually upon each in a portfolio style approach, it is suggested that maximal value can be obtained where all three are managed in tandem. It is argued that the critical link between Exploration and financial reward is Development and that its importance in the literature needs to be highlighted.

Structure of this chapter

The remainder of this chapter will be structured into five sections. The first section will outline the triad of protagonist processes, which are labelled: *Exploration*,

Development and Use for Appropriation. In this section the complementary and antagonistic relationship that exists between these three processes is also outlined. Four propositions on the relationship between Exploration, Development, and Use for Appropriation and the financial value of the firm are offered in this section. These propositions, while not critical to this thesis, do offer insight into both Chapters Three (Celltech case analysis) and Four (event study). The second section will briefly contrast the Exploration/Exploitation dilemma with Nonaka's knowledge spiral. It is argued that Nonaka's knowledge spiral is not the same concept as knowledge Exploration/Exploitation. It is suggested that Nonaka's knowledge spiral conversions from tacit knowledge²⁶ to explicit knowledge²⁷, and visa versa, can occur within Exploration, Development, and Use for Appropriation individually. The third section will outline the three antagonistic meta-processes that are in conflict with the protagonists. These are labelled. *Core Rigidities*, *Slow Rate of Learning*, and *Imitation*. This section shall also outline the complementary relationship that exists between these three processes. At this stage the relationship within and between protagonist and antagonist processes will be summarised in Figure One. The fourth section will explain how changes in level and nature of three dynamic characteristics of the firm can trigger movement from protagonist processes to their antagonist and visa versa. These are labelled. *Intellectual Diversity*, *Social Interaction*, and *Codification*. The movement between each protagonist and antagonist will be outlined in a series of figures (two to four) The complementary and antagonistic relationship that can exist between these three dynamic characteristics of the firm shall also be outlined. The final section will summarise the relationships between the protagonist and antagonist processes and dynamic characteristics of the firm in an overall framework (Figure Five).

²⁶ Nonaka and Takeuchi (1995) note that there are two dimensions to tacit knowledge. "the first is the technical dimension, which encompasses the kind of informal and hard-to-pin-down skills, or crafts captured in the term know-how The cognitive {second} dimension of tacit knowledge reflects our image of reality (what is) and our vision of the future (what ought to be) Though they cannot be articulated very easily, these implicit models shape the way we perceive the world around us" (Nonaka and Takeuchi 1995)

²⁷ Explicit knowledge can be defined as that which can be written or explicitly communicated to others

EXPLORATION/EXPLOITATION AS A TRIAD: EXPLORATION, DEVELOPMENT AND USE FOR APPROPRIATION

This chapter is concerned with three meta-processes. First is Exploration, or the search for and integration of new stocks of knowledge into the firm. This can be linked to the concept of outward looking absorptive capacities (Cohen and Levinthal, 1990). Second is Development, or the extension of the current stock of organisational knowledge. Extension of current stocks of knowledge is heavily effected by the descent of learning and experience curves (Darr, Argote, and Dennis, 1995; Epplé, Argote and Devadas, 1991; Petrakis, Rasmusen and Roy, 1997) where knowledge about the efficient production of a given product or service, or the management of a given process incrementally grows over time. Development may also involve incremental development of a stock of knowledge that is not based upon riding down an experience curve. Third is Use for Appropriation, which involves the use of current stocks of knowledge to appropriate a financial return for the organisation. Such returns may be derived from the sale of final product, such as a consumer drug, or intermediary products, such as licensing of a patented drug. Appropriation is facilitated by inward looking absorptive capacities, which facilitate speedy transfer of knowledge across intra-organisational boundaries (Cohen and Levinthal, 1990) and knowledge articulation, where tacit knowledge is converted into explicit knowledge (Nonaka, 1994). Both of these processes facilitate speedy embedding of knowledge into products and services that can be sold to external customers.

Exploration

As noted earlier, Exploration is defined by Levinthal and March (1993) as “the pursuit of new knowledge of things that might come to be known” It is important to link this definition to Levinthal’s seminal work with Cohen on Absorptive Capacities (Cohen and Levinthal 1989, 1990, 1994). Cohen and Levinthal (1990) define absorptive capacities as “the ability of a firm to recognise the value of new, external information, assimilate it, and apply it to commercial ends.” They note that “the ability to evaluate and utilise outside knowledge is largely a function of the level of prior related knowledge. At the most elemental level, this prior knowledge includes basic skills or

even a shared language but may also include knowledge of the most recent scientific or technological developments in a given field. Thus, prior related knowledge confers an ability to recognise the value of new information, assimilate it, and apply it to commercial ends.”

Cohen and Levinthal sub-divide absorptive capacities into outward and inward looking categories. Outward looking absorptive capacities incorporate the ability to recognise and assimilate external knowledge into the firm. This is at the heart of the process of Exploration which Levinthal and March (1993) proposed. It is important, however, to recognise that the stock of new knowledge created by the firm can be discovered not only by an external search of the environment and subsequent absorption, but also from a recombination of knowledge that resides inside the firm. In essence this takes account of Kogut and Zander’s (1992) combinative capabilities. The firm’s knowledge stock can be increased through reliance upon its own creative minds, resources and capabilities, to generate new organisational knowledge rather than external stimuli. The knowledge created by the method may well be known outside the domain of the firm, however the firm has chosen to develop it independently, perhaps due to the lack of an outward absorptive capacity to recognise and assimilate the knowledge, practical impediments (such as Intellectual Property Rights), or the effect of Not-Invented-Here syndrome. Thus Exploration may involve the use both of absorptive capacities, or external search and assimilation, and internally focused knowledge creation activities.

Exploration is defined as activities that seek to create new stocks of organisational knowledge through the search for and assimilation of new knowledge originating from the external environment, or through internal research activities. Exploration that involves external search must also have an ex-ante goal of assimilation of new knowledge obtained into the firm’s stock of knowledge.

At its heart the process of Exploration seeks to create new opportunities for the firm to create new technologies or processes. Exploration is about improving the flexibility of the firm through the creation of new stocks of organisational knowledge. New stocks

of knowledge broaden the firm's ability to react to, exploit, or shape, changes in its external environment.

Development

The Levinthal and March (1993) definition of Exploitation contains two elements. They define Exploitation as "the use and development of things already known." Unfortunately these two distinct concepts appear to be used interchangeably after initial definition, yet they are clearly separate processes with distinguishable goals. It is important to separate Development from Use for Appropriation. Development, or deepening, of current stocks of knowledge is triggered by investments in learning by doing (Hatch and Mower, 1998). The goal of development is clearly to expand the firm's current stock of knowledge. Use of knowledge in the context of the Levinthal and March concept of Exploitation clearly has a different goal, namely the use of the current stock of knowledge to appropriate an economic return for the firm. Thus Development is focused upon the expansion of the current stock of knowledge and Use for Appropriation with the appropriation of a financial return.

It is an obvious point that complex administrative routines and organisational capabilities, may be developed by firms but that the knowledge embedded in these is of no value if it cannot be profitably embedded in an end product or service sold into the external environment (Hamel and Prahalad, 1990; Kogut and Zander, 1992; Mathur and Kenyon, 1998). Thus there is a clear link between Development and Use. Similarly there is a clear link between the Exploration for new knowledge, the Development thereof and eventual use. Levinthal and March clearly recognised that while related to each other, Exploration is distinct from Exploitation. This chapter argues that the same should apply to Development and Use for Appropriation. Thus the process of Exploitation is split into two distinct, but related, processes, referred to as *Development* and *Use for Appropriation*. An important argument of this chapter is that Development acts as a linkage between Exploration and Use for Appropriation and as such it should not be ignored.

Development is defined as activities that seek to expand, or reconfigure, the current boundaries of stocks of organisational knowledge through a process of deepening understanding of the current stock of organisational knowledge by learning associated with the descent of experience curves. The goal of Development is the expansion of a firm's stock of knowledge into formats that facilitate Use for Appropriation. Development identifies opportunities that exist within a firm's current stocks of knowledge to realise efficiency improvements, new products or product extensions and convert those opportunities into knowledge amenable to Use for Appropriation.

At its heart the process of Development is about exploiting gains from specialisation by squeezing more value adding opportunities from a firm's current stock of knowledge. Development, or deepening, brings with it the benefits of increased specialisation, while Exploration brings with it the benefits of flexibility through increased breadth of pools of knowledge.

The link between Exploration and Development

There is a clear link between the processes of Exploration and Development. Without a stream of new knowledge created by the process of Exploration, Development activities will eventually fail to expand the firm's current stock of knowledge. In common with Economies of Scale curves where eventually the curve can theoretically rise and diseconomies occur, experience and learning curves can tail off or rise and dis-economies of Development can emerge. Thus, Development on its own is not enough to sustain expansion of a firm's knowledge stocks in the long term. Equally as argued above Exploration requires Development for new knowledge to be converted into a format that can be efficiently and effectively used for appropriation. A knowledge stock that expands more rapidly than competitors' stocks is not of value to the firm unless it can be effectively used for appropriation.

If Exploration is not linked to the process of Development then it will be difficult to convert the outputs of Exploration into products and services that add value for the firm. In such a scenario Exploration is disconnected from Exploitation. New stocks of

knowledge, created through the process of Exploration, are not integrated into the firm's current organisational systems, thus such knowledge is either not applied, or to be applied a separate organisational structure needs to be created to facilitate its Exploitation. One can imagine that circumstances may arise where such separation is prudent, however, in general a firm could not profitably exist if new structures and systems had to be created each time new stocks of knowledge were created.

Exploration as disconnected from Development: the case of Xerox PARC

An interesting example of such disconnection is that of Xerox PARC. In the 1970s Xerox created a research centre at Palo Alto, called Xerox PARC. Its function was essentially to Explore new technologies in the area of the paperless office, which represented a considerable long term challenge to Xerox's domination of the photocopier sector²⁸. The goal of Xerox PARC was to "invent systems that could support executives, secretaries, salesmen, and production managers in what became known as the 'office of the future'." (Smith and Alexander, 1999). Xerox PARC created some amazingly advanced products for its time, such as the first Personal Computer, called the Alto (in 1973), the first word processing programme, the first Graphical User Interface complete with mouse pointing device, the first Local Area Network and the first laser printer (Xerox PARC, 1999).

Xerox PARC also had as a stated goal the transfer of promising technologies to Xerox, which could then be exploited by the parent company (Smith and Alexander, 1999). Technologies that had promise in the domain of imaging were successfully exploited by Xerox, however large tracts of technology, for example the Personal Computer, that were removed from the technological and cultural core of Xerox were never successfully exploited by the firm. Others were, however, quick to realise the commercial potential of knowledge explored at Xerox PARC and moved fast to

²⁸ Readers who wish to obtain more detailed information on the fascinating history of Xerox PARC, in particular its role in the foundation of the Personal Computer sector, are referred to Smith and Alexander's (1999) very readable book entitled *Fumbling the Future How Xerox invented, Then Ignored, The First Personal Computer*, San Jose: toExcel Information on Xerox PARC's on-going activities can be found on the company's web site ([http //www parc xerox.com](http://www.parc.xerox.com)).

develop and exploit it in the market. For example Xerox PARC demonstrated the Alto to Steve Jobs in 1979, who in turn promptly hired key Xerox PARC staff to create the Apple II. The creation of the Apple Lisa computer, launched in 1983 and a forerunner of the Apple Mac was fuelled by Jobs' visit to Xerox PARC (Carlton, 1997).

Viewing the experience of Xerox PARC in the 1970s from the perspective of knowledge Exploration/Exploitation one could argue that the problem for Xerox PARC was that the management of Exploration activities were largely unconnected to Development and Use for Appropriation. The technologies created by Xerox PARC were disconnected at both a technological and cultural level from the then current photocopier and paper office knowledge base of Xerox. Holusha (1998) noted that "one of the distinguishing characteristics of Xerox is that, as a corporation, it still believes in the value of research." He notes that Burgelman, who consulted widely for Xerox in the 1980s, believes that the reason for the failure of Xerox to convert the knowledge created through the Exploration activities of Xerox PARC was that "the company has many functional managers immersed in the details of its reprographics operations, but few general managers to look afield." Smith and Alexander's (1999) book on Xerox PARC and the creation of the Alto PC is rich in quotations that illustrate that not only the technology, but more importantly, the culture and management style of Xerox PARC was radically different from that of Xerox. There appeared to be a lack of managerial linkages between the Exploration of Xerox PARC and a vision of how this knowledge could, or should, be integrated into and developed by Xerox itself.

Today, Holusha (1998) argues, Xerox is more successful at exploiting the research of Xerox PARC because they seek "to tie its research more closely to product development." Managers inside Xerox PARC also note that today there is a much greater congruence between the culture of Xerox PARC and Xerox itself. In the 1970s Exploration was the goal of employees inside Xerox PARC. Development and commercialisation was largely disdained. Today employees inside Xerox PARC are more inspired by the image of Bill Gates and aim to link Exploration of new ideas to

commercial Exploitation of those ideas through the powerful commercial vehicle of Xerox itself than the pursuit of pure science alone (Holusha, 1998).

Because the Exploration activities of Xerox PARC were not connected to main activities of the firm via Development, Exploitation by Xerox would have either required radical upheaval in the core reprographics business to enable cultural and technological accommodation of the ideas generated by Xerox PARC, or for separate organisational structures to be created to develop and appropriate a return from these ideas. This portfolio approach, where Exploitation is separated from Development and Use for Appropriation is the way Xerox tackled this problem (Holusha, 1998). It set up a venture capital division that provides seed capital to Xerox employees to set up their own firms to exploit ideas that emerge from Xerox PARC. Thus Development is largely undertaken by those who explored the idea in the first place, but is also conducted outside the boundaries of Xerox. This approach has only created ten firms so far, with varying levels of success (Holusha, 1998). This solution is, however costly. New structures need to be formed. Xerox cedes 20% of the equity to management, but puts up 100% of the seed capital. Its control over the technologies created by PARC is lessened.

Exploration and Development as complements and antagonists

The link between Exploration and Development is important and complementary, both have the goal of expanding the stock of knowledge and each requires the other to prosper in the long term. Without an injection of new stocks of knowledge from Exploration activities Development will eventually encounter negative economies of incremental knowledge creation. Without Development, Exploration activities will be viewed as operating outside the firm. Integration of such knowledge will require new organisational systems and structures, such as a new subsidiary company to be created for the purposes of effective exploitation. If Exploration activities are linked to Development, then new knowledge stocks can be incrementally infused into the firm, minimising organisational disruption, while ensuring that the firm does not stagnate.

The relationship between Exploration and Development is not, however, exclusively complementary. The two processes can also be in conflict with each other. Exploration seeks to increase flexibility and overcome the negative effects of specialisation caused by Core Rigidities. Development seeks to reinforce the gains from specialisation in capabilities. In a firm with finite resources and capabilities there will arise a conflict between those who seek to invest in external search and those who support the internal development of organisational knowledge. While overlaps do exist there is likely to be a natural bias towards the support of internal development, over Exploration. This is because often the benefits from Development are more immediately obvious. Incremental extensions of current processes are more easily understood than the creation and assimilation of new knowledge with which the firm has a lower degree of familiarity.

Distinguishing Development from Use for Appropriation

Development is an important knowledge creation activity and, while linked to Use for Appropriation, it is also distinct from it. Knowledge may well be created within the Development activities of a firm that is subsequently not used for appropriation. This may be because the knowledge proves unsuitable for appropriation within the firm and is abandoned during the Development process, or alternatively because superior appropriation opportunities arise over time making some developments uneconomic.

In essence once the firm has created new organisational knowledge, whatever the source, development involves the firm being efficient at riding down its learning and experience curves. There is a considerable body of literature on the value of learning and experience curves (Arrow, 1962; Dorroh, Gulledge and Womer, 1994, Hatch and Mowery, 1998; Henderson, 1974; Hirsch, 1952; Lieberman, 1984; Petrakis, Rasmusen and Roy, 1997; Rapping, 1965; Wright, 1936, and Yelle, 1979). The essence of this literature is that as a firm becomes more familiar with a given technology, process, or administrative routine through usage it gains insights that enable it to become more efficient and effective at the task. These insights may enable the firm to make incremental improvements in technology or working practices. Such tasks lie at the

heart of the process of Development, or knowledge deepening, and are related to, but distinct from, either Exploration or Use for Appropriation.

Use for Appropriation

Use for appropriation is defined as activities that seek to leverage the firm's current stock of organisational knowledge as effectively as possible in the marketplace either by distribution of cost or informational advantages across the firm or deployment of superior products and services in the marketplace. Either activity brings direct financial rewards from the firm's current stock of organisational knowledge.

At the heart of appropriation is tangible action to deploy benefits derived from either Exploration or Development across the firm or in the marketplace to obtain financial returns. The goal of Use for Appropriation is to appropriate an economic return from the firm's current stock of knowledge, as created through the processes of Exploration and Development. New knowledge may incidentally emerge from Use for Appropriation, however appropriation of an immediate financial return rather than expansion of the firm's current stock of knowledge is the primary goal of this activity. An example of Use for Appropriation is the launch of a new product in the marketplace, or the introduction of a cross departmental and regional information sharing database to disperse knowledge about cost saving processes and market opportunities across the organisation.

The process of Appropriation is linked to Cohen and Levinthal's concept of inward looking absorptive capacities. Inward absorptive capacities can be viewed as the firm's ability to assimilate and *commercially exploit* the firm's current stock of knowledge. This process requires that relevant knowledge be communicated within departments of the firm in addition to the assimilation of key organisational knowledge across departments. It is not sufficient that the processes of Exploration create and assimilate new knowledge and the process of Development incrementally deepens the firm's stock of knowledge. If the goal of the firm to obtain economic rent is to be achieved then it is important that this knowledge does not remain in isolated parts of the firm,

rather that it is speedily distributed to all parts in which it can be profitably employed and products be quickly and effectively deployed in the marketplace.

There is an immediate tension between the processes of Exploration and Use for Appropriation, similar to that identified in the classic Exploration/Exploitation dilemma. In essence there is a tension between the short-term need for positive cash flows, which the Use for Appropriation process brings, and the more long-term search for and creation of new knowledge that Exploration offers. This tension is partially due to the conflict between outward and inward looking absorptive capacities. As Cohen and Levinthal (1990) state “with regard to the absorptive capacity of the firm as a whole, there may be a trade off in the efficiency of internal communication against the ability of the sub-unit to assimilate and exploit information originating from other sub-units or the environment. This can be seen as a trade-off between inward looking versus outward-looking absorptive capacities. While both of these components are necessary for effective organisational learning, excessive dominance by one or the other will be dysfunctional.”

The pay-off from inward looking absorptive capacities is likely to be known quickly. There are tight feedback loops between the dissemination and assimilation of knowledge from one part of the firm to another and the profitability thereof. If carefully monitored the firm can establish in the short to medium term if the transfer of administrative routines, or capabilities from one sub-unit to another has resulted in cost savings, or the ability to deploy current products and services in new markets, resulting in improved sales performance. The effects of outward looking absorptive capacities are more long term. The search for new valuable knowledge is both time consuming and its outputs uncertain. The assimilation of that knowledge into the firm takes more time, and is likely to be more difficult to assimilate and apply than knowledge created via the process of Development, due to its alien nature. Once assimilated only then can the process of wide scale Use for Appropriation occur.

Propositions: value added and knowledge Exploration/Exploitation.

The above discussion argues that Exploitation should be separated into two related, but distinct, factors: Development and Use for Appropriation. Levinthal and March's (1993) definition of Exploitation recognises these two factors, but the literature does not appear to discuss the two factors in-depth or separately. The first proposition offered is thus:

Proposition One: Exploitation is more fully characterised as two related, but distinct processes: Development and Use for Appropriation. It is possible for both concepts to be separately identified and measured in real organisational contexts. It is then possible for each factor to be assigned a value by the market.

This proposition is explored in Chapters Three and Four. In Chapter three the activities of Celltech are classified as Exploration, Development and/or Use for Appropriation. Simple measures of each activity are created and applied to the Celltech case over a period of a decade. In Chapter Four the impact of announcements of Exploration, Development and/or appropriation events by UK therapeutic biotechnology firms upon share price is analysed. It is found that the value assigned by shareholders to announcements of events in these three categories is different.

For the second empirical exploration of proposition one to be possible then the market must assign a value to both Exploration and Exploitation activities. As noted earlier, prior literature has argued that there is a bias towards Exploitation activities due to clearer and shorter financial feedback loops. It has been argued above that Exploration plays an important role in the long term survival of the firm. Without an infusion of new stocks of knowledge created by the process of Exploration the firm will in the long term stagnate and be overcome by more innovative rivals. From this argument it follows that both Exploration and Exploitation should be financially valuable. Thus the second proposition offered is:

Proposition two: Both Exploration and Exploitation activities generate financial value for the firm. It is possible for this financial value added to be estimated from individual

announcements of the outputs of Exploration, Development and Use for Appropriation activities in an independent firm with relatively few projects.

This proposition is jointly explored with proposition one in Chapter Four. It is found that it is possible to apply the event study methodology to this sector and conceptual problem. Differences between the value of announcements of Exploration, Development and/or Use for Appropriation events are observed in Chapter Four.

Given the increasing length and causal ambiguity of feedback loops, the temptation for management will be to invest in descending order in Use for Appropriation, Development and Exploration. Thus, without careful management, investment in the process of Exploration declines over time, effectively ensuring the onset of Core Rigidities, as outlined in the following section. The danger that such a policy poses is noted by Cohen and Levinthal (1990), who state that “the cummulativeness of absorptive capacity and its effect on expectation formation suggest that an extreme case of path dependence in which once a firm ceases investing in its” {outward looking} “absorptive capacity in a quickly moving field, it may never assimilate and exploit new information in that field, regardless of the value of that information.”

It is important to note that for the firm to successfully manage its organisational knowledge it needs to recognise that globally these protagonist processes also feed into each other. As was outlined above there is a clear interconnection between the processes of Exploration and Development. For the process of Use for Appropriation to operate there must be knowledge generated by the process of Development before it can be distributed throughout the firm and integrated into products and services. Thus it is that creation of new stocks of knowledge (Exploration) via outward looking absorptive capacities and internal new knowledge creation activities combine with the extension of current stocks of knowledge (Development) to be exploited through inward looking absorptive capacities and the process of Use for Appropriation. Kogut and Zander (1992) hint at the natural circular interaction between the processes of Use for Appropriation, Development and Exploration when they state that “an important limitation to the capability of developing new skills is the opportunity (or potential) in

the organising principles and technologies for further Exploitation. Eventually there are decreasing returns to a given technology or method of organising and there, consequently, results an incentive to build new, but related skills.” Essentially the firm develops and appropriates a return from a technology to the extent that it cannot be usefully developed anymore. In an effort to seek complementary routines or capabilities to augment the technology the firm engages in a process of Exploration for new ideas. This may trigger new leads that can be followed up through the process of Development and incrementally improved into a new complementary set of skills or technologies, which in turn can feed into the process of Use for Appropriation. Thus a third proposition is offered:

Proposition Three: The value generated by a firm will be greater when the processes of Exploration, Development and Use for Appropriation are managed as an inter-dependent set of activities than when managed as a portfolio of three separate activities.

This proposition is briefly explored in Chapter three. It is argued that the renewal of Celltech is partially attributable to the management’s efforts to be innovative in managing the linkages between Exploration, Development and use for Appropriation. Whereas in the Celltech of the 1980s Exploration was separate from Development and Use for Appropriation, in the 1990s the management connected these activities through a series of review systems. They also initiated a series of innovations that generated signals about the potential value of drugs being created inside the firm’s Exploration processes. The principal signally mechanism employed was a series of alliances with firms amongst the top twenty largest pharmaceutical firms in terms of turnover in the world. Such signals facilitated valuation of Exploration activities by shareholders, thus creating a visible financial feedback loop not only for Exploitation activities but also Exploration.

An implication of proposition three is that, contrary to prior theoretical arguments, balance between Exploration and Exploitation can be maintained in the medium to long term. This is an extension of the argument that Exploration, Development and

Use for Appropriation should be managed as an inter-dependent system. If Exploration/Exploitation is managed as an inter-dependent system then it should be possible for a balance to be maintained across the system. Thus a fourth proposition is offered:

Proposition Four: Where balance between Exploration and Exploitation is maintained over the long term then value added is greater than when the dilemma is managed by a series of periods, where Exploration dominates in one and Exploitation in the other.

The literature argues that Exploitation tends to dominate over Exploration in the long term, due to clearer feedback loops and greater short term financial gains (Levinthal and March, 1993). Taking this assumption as fact implies that firms must periodically engage in costly restructuring, where new ideas are infused into the firm by moving from Exploitation back to Exploration or face extinction as of new technologies and processes created by rivals emerge and transform the nature of competition. Proposition four argues that if management could solve this dilemma and maintain balance then the firm should be more competitive. It would not have to incur the costs of period re-structuring that would accompany movements between domination of Exploitation and Exploration. Instead the firm would be balanced, exploiting current stocks of knowledge and managing the search for and assimilation of new stocks of knowledge, the future of the firm, in an orderly manner.

NONAKA'S KNOWLEDGE SPIRAL AND EXPLORATION/EXPLOITATION

Some people have noted that Nonaka's knowledge creation spiral, which consists of four processes of knowledge conversion, namely, socialisation (tacit to tacit knowledge conversion), articulation (tacit to explicit), combination (explicit to explicit) and internalisation (explicit to tacit) could be categorised into Exploration, Development and application²⁹. However multiple elements of this spiral of knowledge creation can occur within each of the three meta-processes of Exploration,

²⁹ For a detailed discussion of Nonaka's spiral of knowledge creation the reader is referred to Nonaka, 1991, 1994 and Nonaka and Takeuchi, 1995.

Development, and Use for Appropriation. Articulation can be seen to be valuable in Use for Appropriation as it speeds up transfer of knowledge suitable for appropriation across the organisation quickly. However internalisation could also play an important role. Once the knowledge has been distributed throughout the organisation then internalisation may speed up use of the knowledge considerably as Nonaka notes that tacit knowledge is applied at an intuitive level, and hence faster rate (Nonaka, 1991).

In the case of Development the processes of articulation, combination and internalisation can all play a valuable role in exploiting the benefits of experience. In the early stages of experience with a product or process, articulation may be very important. Ensuring that all actors have a clear understanding of how the process or product works by explicitly understanding its production or operation enables the firm to deepen specialist knowledge. Conversion from tacit to explicit knowledge enables the firm to move from a craftsman approach to management of a stock of knowledge to a more production line approach, which facilitates riding down the experience curve. Gaining an explicit understanding of a process as a whole enables its division into areas of specialism, the creation of a knowledge 'production line' thus driving the firm down the experience curve. Combination of two forms of explicit knowledge may enable incremental improvements to be made, thus driving the firm further down the experience curve. As staff become more familiar with a product or process they begin to internalise their knowledge of it, thus converting explicit process knowledge into tacit. This process of internalisation may trigger fresh insights into how the product or process can be made more efficient, thus propelling Development forward even further and driving the firm down the experience curve.

One could take military aircraft development during World War II as an example of these three processes in action. One can imagine that at the beginning of the war production of aircraft was a near craft process. The technology of aircraft was relatively new, and its application in warfare relatively limited. As the war intensified craftsmen were drawn away from production and into the war itself. Women entered the workforce, forcing a conversion of craftsmen's tacit knowledge into explicit knowledge (articulation) such that non-specialists could operate production lines. As

women on the line became more familiar with the aircraft production process they internalised that knowledge enabling faster decent of the experience curve. Such internalisation would have also brought with it insights into how aircraft could be produced more efficiently. This knowledge could in turn be articulated to management enabling alterations in production techniques, and hence greater efficiency gains. Thus the spiral of knowledge creation combined with incremental decent of learning curves enabling a female workforce that was initially unfamiliar with the process of military aircraft production to, over time, achieve considerable improvements in both the efficiency of production and the effectiveness of the product they produced.

Combination of explicit knowledge from two sources can also spur Development. The Celltech case is a good example of Development through combination. Celltech and Bayer combined their patent portfolio in the area of antibodies that produce TNF (Tumour Necrosis Factor). The combination of these two patents, which can be classified as explicit knowledge, enabled the firms to create an “almost impregnable position around TNF” in terms of legal protection (Dr Yarranton, Celltech case study). This combination of patents provided important additional knowledge about anti-TNF technology, which propelled the development of a new drug forward.

The process of Exploration can also be linked to Nonaka’s spiral of knowledge creation. The processes of articulation and combination are particularly relevant in knowledge Exploration (Nonaka, 1994). Articulation of tacit knowledge from an external source into explicit knowledge that can be used inside the firm would be a good example of Exploration. Such articulation can be found in the Oxford Molecular case study, which is in the appendices of this thesis. Yamanuchi, a large Japanese pharmaceutical firm, entered into an alliance with Oxford Molecular for the purpose of transferring knowledge about ION channels and their application to disease management from university research centres, through Oxford Molecular, and into Yamanuchi. Much of this knowledge was tacit in nature, held in the heads of individual researchers within UK universities. The goal of Oxford Molecular was to transfer this knowledge from these university researchers into explicit knowledge, which could then be transferred to Yamanuchi. Thus tacit knowledge about the role of

ION channels in a disease was acquired by Oxford Molecular and over time they converted this knowledge into an explicit form, which was transferred to Yamanuchi.

Exploration, Development, and Use for Appropriation are meta-processes shaped primarily by the goal of the knowledge creation activity: to create a new stock of knowledge, incrementally expand a current stock of knowledge, or use for the purpose of appropriation a current stock of knowledge. The form of knowledge conversion under consideration, from tacit to explicit and visa versa shape shapes Nonaka's knowledge creation spiral. Thus while Nonaka's work is of relevance in this chapter, and is referred from time to time, it does not form the principal thrust of the arguments developed in the remainder of this thesis.

ANTAGONISTIC PROCESSES

There are compelling reasons why balance is difficult to maintain. One of the principal reasons for a firm moving out of balance is because each protagonist has an antagonistic process that it is in conflict with and into which over time firms descend in and out of. These antagonistic processes are Core Rigidities, Slow Rate of Learning, and Imitation. Their roots are hinted at across many elements of the literature.

Core Rigidities

Core Rigidities are sets of knowledge, which although valuable now, are inappropriate to future needs of the organisation. Core capabilities can, over time, turn in upon themselves to become Core Rigidities. As Peteraf (1993) puts it: "current capabilities may both impel and constrain future learning and investment activity." The process of Exploration seeks to identify new knowledge upon which new capabilities and routines can be developed to replace the capabilities that have in the past been a source of success, but in the future may become an impediment. Core Rigidities are antagonistic to this process and seek to reinforce the use of current capabilities to the exclusion of Exploration. Exploration seeks to widen the scope of a firm's stock of knowledge, thus increasing flexibility, while Core Rigidities are caused by sustained specialisation, resulting in inflexibility.

At the heart of the process of Core Rigidity is the dilution, and in extreme cases, extinction of outward looking absorptive capacities and the internal creation of new knowledge through recombination. The process of Core Rigidity results in a narrowing of the breadth of potential and actual capabilities that the firm has at its disposal. This is because the development of core capabilities tends to be path dependent (Cohen and Levinthal, 1990 & 1994; Collis, 1991; Mahoney, 1995). By concentrating ever more on the maintenance and incremental extension of a narrow, specialised, range of capabilities that are developed internally, the firm may under invest in outward looking absorptive capacities, or re-focus internal research activities away from creation of new technologies and processes. Increased specialisation also reduces the breath of capabilities, which may be the source of new knowledge creation through recombination. No matter how large and diverse the firm is, without stimuli from external sources, it will eventually run out of ideas upon which to develop new capabilities. In this scenario the firm would stagnate, losing the ability to generate new capabilities to replace the old, due to a critical lack of understanding of the new technologies, or administrative routines, upon which competition in the external environment is now based. In this circumstance the firm becomes permanently marooned and will, over time, either withdraw from the market in which its capabilities are no longer relevant, or be forced from that market due to inefficiencies in production and/or customer selection.

Slow Rate of Learning

The antagonist to Development is Slow Rate of Learning. Whereas Core Rigidities impede the firm's ability to maintain outward looking absorptive capacities, Slow Rate of Learning impedes a firm's ability to incrementally improve the firm's current stock of knowledge. The principal effect of a Slow Rate of Learning is to impede a firm's descent down its learning and experience curves. The firm becomes relatively slower at this task than its competitors.

Hatch and Mowery (1998) note that the benefits of the learning curve do not occur automatically as a result of increased production experience, but require deliberate action to reduce costs and improve yields over time. Behind the learning curve effect is a host of knowledge combination and re-configuration actions as represented in Nonaka's knowledge creating spiral (Nonaka, 1994; Nonaka and Takeuchi, 1995). Nonaka (1991) notes that critical to the process of knowledge creation are articulation (tacit to explicit knowledge conversion) and internalisation (explicit to tacit). These activities are also crucial to Development, as noted in the previous section of this chapter. Over time a firm may become complacent and believe that its current systems are as efficient and effective as they need be. Alternatively staff may become settled and unwilling to exchange knowledge with those outside their immediate social circle. These attitudes slow the spiral of knowledge creation as outlined by Nonaka. Withdrawal from re-configuration of the current pool of organisational knowledge that the spiral of knowledge creation embodies is referred to, in this chapter, as a Slow Rate of Learning. It results in sub-optimal decent of learning curves and thus impedes the process of Development, hence slowing the growth of a firm's stock of knowledge.

This slower pace of Development may be offset by superior outward looking absorptive capacities, thus enabling the firm to compensate for slow internal development and learning, with relatively faster learning from others. Slow Rate of Learning could also be overcome with relatively faster inward absorptive capacities. This would enable the firm to be relatively faster than rivals at appropriating a return from its comparatively narrower stock of knowledge. However if rival firms are considerably faster at the process of Development then overtime they should outpace the firm in a learning race, accumulating a greater stock of organisational knowledge from which to compete. In the long term survival of a firm is dependent on some degree independent creation (part of Exploration) coupled with Development of organisational knowledge. It is this that enables the firm to generate distinctive competitive advantages from which to produce products and services for which the external environment will financially reward it.

*Imitation*³⁰

The antagonist to Use for Appropriation is Imitation. Every firm that grows commercial knowledge about a specific issue faces imitation by its competitors. Moreover, the greater the level of valuable knowledge, the greater the imitation risk. Imitation, with adaptation, is the natural extension of the process of Exploration. Use for Appropriation is in many ways a competition amongst the firm's inward looking absorptive capacities and rivals' outward looking absorptive capacities. It is reasonable to suggest that as a firm develops valuable organisational knowledge rival firms' outward looking absorptive capacities will search that knowledge out, seeking to identify, understand, improve and internalise it for their benefit. Such imitation by competitors places pressure on the firm's inward absorptive capacities to become ever quicker at the dissemination of knowledge generated in one sub-unit of the firm to other relevant sub-units and its assimilation by those sub-units, thus enabling wider appropriation of a return from that organisational knowledge. In extreme cases the antagonistic process of Imitation by competitors may overload the firm's inward looking absorptive capacities.

Nonaka and Takeuchi (1995), comment that unless key knowledge becomes explicit, or codified, then it cannot be easily leveraged by the organisation as whole in the creation of value added. Effective appropriation requires much of the technical and organisational knowledge of the firm to be stored explicitly, or in detailed organisational routines and procedures. Attaining these goals efficiently pressures the organisation towards codification of its knowledge base.

The paradox of the process of Use for Appropriation is that to efficiently integrate knowledge into the product and service offerings of the firm it will tend towards codification. In so doing it increases the risk that its knowledge will leak out of the firm and be captured by rivals' outward looking absorptive capacities. Thus efforts to

³⁰Imitation does not imply just the copying another firm's knowledge bases, but involves taking some of the best concepts of another firm's ideas and improving upon them (Kogut and Zander, 1992; Schnaars, 1994).

improve the process of Use for Appropriation may simultaneously encourage imitation by competitors.

Complementarity of Antagonists

The challenge posed by the antagonistic processes is further complicated by the fact that each antagonist may be complementary to the other. A core rigidity may develop from sustained Development and be reinforced by a Slow Rate of Learning. When faced with an agile competitor the temptation may be to dig deeper into the old ways of doing business. This is the classic problem of doing what one does better, being more efficient at delivering products and services employing current techniques, rather than doing what one does differently, incorporating new techniques, and thus becoming both more effective *and* efficient. In the face of reduced returns brought on by Imitation one may sink further into a core rigidity response. This complementarity across antagonistic processes means that if a firm descends into a cycle of two, or more antagonistic processes then it may be very difficult to turn the system back to a situation in which the protagonist processes dominate. This has important implications for proposition three of this chapter. Given the interconnectivity of antagonistic processes it is important that Exploration, Development and Use for Appropriation be managed at the higher management level as a unified whole, rather than as a set of three separate portfolios. To manage them completely separately ignores that problems that arise in one process are likely to have a negative impact upon the others.

The antagonism between the processes of Exploration, Development and Use for Appropriation on the one hand, and Core Rigidities, Slow Rate of Learning and Imitation on the other hand, is summarised in Figure One. Figure One outlines the complementary and antagonistic nature of these relationships. Particularly important is the opposite effect that protagonist and antagonist processes have upon absorptive capacities and learning/experience curves. As can be seen, while absorptive capacities have a positive effect upon Exploration and Use for Appropriation, Core Rigidities and Imitation have negative effects upon absorptive capacities. Similarly while decent of learning curves has a positive effect upon Development, Slow Rate of Learning has a

negative effect upon decent of learning curves. Thus the antagonistic processes have the potential to impede, or overload, the protagonist processes by undermining absorptive capacities and decent of learning or experience curves. The box surrounding Development and Use for Appropriation recognises that these combined are what Levinthal and March (1993) defined as Exploitation. It can be seen from Figure One that Exploration has both a positive, or complementary, and negative, or antagonistic, relationship with both aspects of Exploration, namely Development and Use for Appropriation. Figure One also illustrates that the antagonistic processes of Core Rigidities Slow Rate of Learning and Imitation all have positive or complementary relationships with each other. This chapter will now turn to a discussion of what, over time, can trigger movements between protagonist and antagonist processes.

INSERT FIGURE 1 ABOUT HERE

SOME PIVOTAL CHARACTERISTICS IN THE ANTAGONISTIC NATURE OF KNOWLEDGE MANAGEMENT

This section discusses how three characteristics of the firm, labelled Intellectual Diversity, Social Interaction, and Codification of Knowledge, can be manipulated to limit the negative impact of the three protagonist processes, namely Core Rigidities, Slow Rate of Learning and Imitation. Such manipulation can facilitate the dominance of Exploration, Development and Use for Appropriation.

Movements Between the Processes of Exploration and Core Rigidity (Figure Two)

An important question is how are Core Rigidities promoted within the firm and how can management stimulate a re-emergence of Exploration as the dominant process? It is argued that changes in the levels and distribution of a characteristic of the firm, labelled Intellectual Diversity can stimulate movement between these processes.

It is widely argued that the process of Exploration is more likely to occur in a firm that contains individuals, or coalitions, who have several different perspectives. These

could be diverse knowledge bases on how to conduct specific tasks (e.g. production of a product) or differing perspectives on the strategic direction of the firm. This diversity will highlight ways in which the knowledge embedded in the organisational code is 'incorrect'. Diversity of perspectives and individual knowledge bases may suggest novel combinations of the firm's current resources and capabilities, thus avoiding stagnation (Herriott, Levinthal and March, 1985; Levinthal and March, 1981).

If such Intellectual Diversity is not present then neither the creation of new knowledge through internal knowledge creation nor outward looking absorptive capacities could occur. Diverse and curious minds propel the firm towards Exploration of new technologies and organisational routines or processes which are complementary, or even counter, to the ones that are promoted by the current organisational orthodoxy (as expressed in the organisational code and culture). For the process of Exploration to be successful it is not sufficient that diverse perspectives exist, those who hold different ideas from the firm's current orthodoxy need to be encouraged to actively pursue them.

Diversity is injected into the firm by Mavericks, people who dare to think differently to, or are slow to become indoctrinated by the perceived organisational orthodoxy, and personnel turnover, which injects new ideas into the organisation via new personnel and diminishes the power of other ideas via exit. Unlearning, often stimulated by environmental shocks, also has a role to play. It promotes the casting off of old perspectives of the competitive environment and enables the development of new ones.

On the other hand the process of core rigidity can come to dominate Exploration where: there are perceived, and/or tangibly, high switching costs involved in changing core capabilities (Kogut and Zander, 1992); inertia within the organisation, and the high level of uncertainty (and hence cost) attached to investments in Exploration of new knowledge (Levinthal and March, 1993; March, 1991; Huff, Huff and Thomas, 1992). Each of these factors restrict the enactment of a firm's Intellectual Diversity, and thus promote the dominance of Core Rigidities. Their existence encourages members of the firm to continue to apply and expand their current knowledge base to

the problems the firm faces, rather than developing alternative, more effective knowledge bases.

These relationships are pictorially represented in Figure Two. The engine of change, or movement between Exploration and Core Rigidities is Intellectual Diversity, as characterised by the above factors. In Figure Two Intellectual Diversity is split into dynamic and static elements. Mavericks, Personnel Turnover and Environmental shocks are tied to Intellectual Diversity by a line and represent the dynamic elements. Organisational inertia, Switching costs, and High Uncertainty of successful change, are the static elements of Intellectual Diversity. It can be seen that dynamic changes in the firm's Intellectual Diversity, that is the promotion and enactment of diverse perspectives triggered by Mavericks, personnel turnover, and unlearning promotes Exploration. Stagnation of Intellectual Diversity prompted by organisational inertia, switching costs, and high uncertainty, means that fewer new ideas are encouraged and enacted, even where there exists diverse perspectives within the firm, thus promoting the dominance of Core Rigidities. The feedback loop between Exploration and Core Rigidities indicates the negative, or antagonistic relationship that exists between each process. This chapter will now look at Mavericks, personnel turnover and unlearning in more depth.

INSERT FIGURE 2 ABOUT HERE

Mavericks

Mavericks are slow to accept indoctrination into the “the company way”, as represented by the experiences embedded in the organisational code. Such people it is argued, promote diversity of thought within the organisation. In so doing they will increase the likelihood that alternative capabilities will begin to take root. These can be accentuated and developed as elements of current organisational knowledge evolve into a core rigidity.

Mavericks *complement* individuals who learn the organisational code quickly, or 'fit' into the organisation and do things 'the company way'. Quick learners integrate current organisational knowledge into their jobs more efficiently than Mavericks, who expend time questioning. 'Fast learners' may be less effective as catalysts to organisational change than Mavericks. Change is more likely to occur if managers notice a gap between the knowledge that the firm employs and that needed to effectively deliver value to customers. Mavericks are good at this. Questions, which highlight value adding dilemmas or incongruities, are more likely to come from the questioning minds of Mavericks rather than 'company people'.

Encouraging Mavericks brings direct and obvious risks. Their protest against the dominant orthodoxy may lead to serious conflicts, distracting effort from current workflows. Too many Mavericks may lead to an over adaptive organisation, one in which change becomes near continuous and progress down a single path rarely proceeds long enough to appropriate an adequate return. The slow learning of Mavericks may also impede speedier descent down current learning and experience curves, which is critical to the process of Development.

Personnel Turnover

An alternative method of creating diversity is through injection of new ideas by hiring new staff (Carley, 1992; Simon, 1991). Rapidly growing firms are constantly recruiting. New recruits bring with them new ideas and work practices, which can stimulate the process of Exploration. Mature firms that want to become more adaptive, have lower rates of growth and thus can often only increase diversity through personnel exiting the organisation and being replaced by new staff³¹. A personnel turnover strategy requires a careful management of knowledge stocks, such that valuable knowledge stored in departing personnel is substituted through the process of

³¹Downsizing, prevalent in mature organisations since the 1980s, may provide an opportunity and a barrier to turnover strategies. Exiting personnel offer the opportunity to inject new blood into the firm. Equally, introduction of new personnel may encounter considerable resistance, being viewed as inconsistent with the downsizing goals of cost reduction and improved efficiency.

new personnel entering the organisation. Some of the disruptive effects can be avoided if the knowledge is transferred and stored in retrievable fashion within the organisation's routines or remaining personnel.

Use of turnover strategies also requires awareness of the possibility that the departing staff during the 'hand over' period may indoctrinate new staff in knowledge, or behaviours, which the firm's management would prefer extinguished (Javanovic and Nyarko, 1995). As with Mavericks personnel turnover may impede speedier movement down a firm's learning and experience curves, thus while promoting Exploration Mavericks and Personnel Turnover may impede the process of knowledge Development. This is caused by the requirement for new staff to learn how the current administrative routines and capabilities of the firm operate and the lack of acceptance of the current orthodoxy by Mavericks.

Unlearning

As noted above, it is widely recognised that organisational inertia inhibits change and that every successful firm faces extreme difficulties in adjustment. As capability development is path dependent, the removal of Core Rigidities takes time. Behaviours can become deeply embedded and inhibit, rather than promote, actions that add value. The defeat of Core Rigidities will require removal, or extinction of these behaviours. Unlearning is defined by Hedberg (1981) "as a process through which learners discard knowledge" which is "obsolete and misleading" Bettis and Prahalad (1995) and Huber (1991) have noted that unlearning is critical to the broader issue of organisational learning processes. New organisations are less disadvantaged than established firms are because they have less to discard (Hamel and Prahalad, 1994)

The task of 'unlearning' can be viewed as a considerable organisational challenge, because the effort and *risks* involved in switching from one capability to another can be substantial. The interplay between bundles of resources and capabilities necessary to create a new capability will, at the outset, be poorly understood since the creation of

organisational knowledge is by definition a complex and uncertain process. Kogut and Zander (1992) articulate this risk when they note that:

“Switching to new capabilities is difficult as neither the knowledge embedded in the current relationships and principles is well understood, nor the social fabric required to support the new learning known.”

***Movements between the Processes of Development and Slow Rate of Learning
(Figure Three)***

An important question is how is a Slow Rate of Learning promoted within the firm and how can management stimulate the re-emergence of Development as the dominant process? It is argued in this section that changes in the levels and distribution of *Social Interaction* can stimulate movement between these processes.

Many authors have noted that a firm's social system plays an important role in determining the speed and path of learning (Brown and Duguid, 1991; Imai, Nonaka and Takeuchi, 1985; Kay, 1993; Orr, 1990; Simon, 1991). The key features of a firm's social system that shall now be focused upon are the role of organisational slack, common language and experimentation.

Changes in the levels of control of communication flows within firms can increase shared understanding, through increases in organisational slack (Blackler, 1995; Cyert and March, 1963; Huber, 1991; Nonaka, 1991). Language plays a central role in the operation of social systems. For knowledge to be created there needs to be investment in a shared language amongst the individuals involved (Blackler, 1995; Cohen and Levinthal, 1990; DeGeus, 1996; Nonaka and Takeuchi, 1995). Just as academics develop precise codes to facilitate the transfer of ideas among themselves, so people in organisations generally need to express their ideas in terms that others understand. Given the central role of individuals in knowledge creation, without the transfer of knowledge across individuals organisational knowledge would be unlikely to develop to a commercial level, if at all.

Sometimes small changes in Social interactions can result in considerable changes in the efficiency and effectiveness of Development of an administrative routine or capability. This is due to the often causally ambiguous interconnections between bundles of resources, capabilities and human factors that lead to success (Badaracco, 1991; Hall, 1992; Itami and Roehl, 1987). Put simply, routines and capabilities can evolve and be successfully deployed in a black box environment. Management may have a reasonable understanding of the inputs dedicated to the routine or capability and the broad outputs it produces but it remains largely unable to decipher the causal relationships between the inputs which determine the successful delivery of the outputs.

The existence of casual ambiguity can, as will be argued later, play a vital role in the process of Appropriation. Casual ambiguity, however, challenges the ability of management to control the process of Development. Changes in the distribution of organisational slack, the nature of the firm's language, and interactions between functions may unexpectedly impact upon casually ambiguous processes in both a negative and positive manner. The feedback loops between the impact of changes in Social interactions and outputs may be casually ambiguous and thus difficult to assess. This may encourage management to adopt a policy of 'don't fix what's not broken' or excessive caution in changing social systems for fear of long term, and difficult to predict, impacts on the efficiency of the firm. Either policy is likely to slow the rate of learning within the firm.

These relationships are pictorially represented in Figure Three. The engine of change, or movement between Development and Slow Rate of Learning is Social Interaction, as characterised by the above factors. It can be seen that dynamic changes in the firm's Social Interaction, that is the promotion and enactment of dynamic slack, an open common language, and experimentation promotes Development. Stagnation of Social Interaction prompted by static organisational slack, casual ambiguity and closed, multiple sets, of common language within the firm, promotes the dominance of a Slow Rate of Learning. The feedback loop between Development and Slow Rate of Learning indicates the negative, or antagonistic relationship that exists between each process.

This chapter will now discuss slack, common language and experimentation in more depth.

INSERT FIGURE 3 ABOUT HERE

Slack

Slack can be defined as “the pool of resources in an organisation that is in excess of the minimum necessary to produce a given level of organisational output” (Nohria and Gulati, 1996). Two important subsets of this concept are absorbed and unabsorbed slack. “Unabsorbed slack corresponds to excess, uncommitted liquid resources ... absorbed slack ... corresponds to excess costs in the organisation” (Singh, 1986). Absorbed slack can take many forms from excess capital equipment to information overlaps.

Slack is viewed within the literature as both positive and negative. Economic interpretations often view it as an inefficiency. Ghemawat (1991) notes that slack needs to be managed carefully as it can be subject to misappropriation, especially by employees. Empirical studies by Jensen (1986, 1993) argue that firms with large amounts of slack often invest in R&D projects with negative pay back. He draws his evidence from firms in the oil, automobile, photographic and computer technology industries.

Another group of researchers argue that slack is not merely an organisation inefficiency, or an agency conflict, rather that it plays a positive economic role through increased rates of learning, thus promoting the process of Development. Various arguments are proposed within this literature. More slack permits a higher degree of interaction between people, involving higher levels of communication, greater flexibility and experimentation (Huber, 1991; Inkpen, 1995; Kogut and Zander, 1992; Mc Gill and Slocum, 1993; Nonaka and Takeuchi, 1995). Creating overlaps of information and knowledge between organisational actors is another learning stimulant (Cyert and March, 1963; Nonaka, 1991). Slack is also necessary for job rotation,

another way of creating knowledge and a complementary strategy to personnel turnover (Nonaka and Takeuchi, 1995).

There exists an important additional distinction to the concept of slack, namely, static and dynamic slack. Static slack occurs when the excess resources that exist within parts of the firm have become fossilised. At one time that slack may have existed to stimulate the process of Development, however it has served that purpose and is now been appropriated for means that fall outside the economic goals of the firm. This in essence can be the classic agency problem outlined by Jensen (1986, 1993). Dynamic slack involves the management of organisational slack in such a manner that relationships in the firm are monitored in terms of which ones currently need slack to stimulate knowledge sharing and experimentation. Slack is reallocated from areas where fostering such relationships is a lower priority, or where that slack is becoming static, and towards areas of the firm where slack can be allocated to stimulate more efficient Development.

The dynamic management of slack requires careful identification, monitoring and control of absorbed and unabsorbed slack. This can partially offset the dangers of misappropriation by agents, as proposed by Jensen. Such dynamic management of slack is of course quickest in the case of unabsorbed slack. Liquid resources can be used to buy equipment or time necessary for experimentation. Absorbed slack may be slower to move around the organisation. Teams that have had information overlaps or spare time to stimulate knowledge sharing can gradually have their work loads increased by transfer of tasks from a team which has been working at a higher operational efficiency, where it is believed that that team now needs time to stimulate knowledge sharing or experimentation. In each case the movement in slack from one area of the firm to the other needs to be directed, monitored and controlled.

Static and dynamic management of slack does not only mediate the relationship between slack and Development, but also by the volume of slack within the system. The theoretic proposition that there is an inverse U relationship between slack and innovation has existed for some time (Bourgeois, 1981). Recent empirical research has

supported this proposition in terms of unabsorbed slack. Nohria and Gulati (1996) have explained this empirical result by noting that “too little slack is inimical to innovation because it discourages any kind of experimentation whose success is uncertain. Equally, too much slack is inimical to innovation because it breeds complacency and a lack of discipline that make it possible that more bad projects will be pursued than good.” The optimal rate of unabsorbed slack which they found equated to about 5% of a business unit’s annual budget (Nohria and Gulati, 1997). The optimal rate of unabsorbed slack has not been empirically assessed.

Thus it can be said that slack is a complex concept. Slack needs careful management if it is to promote the process of Development. Dynamic management of slack, coupled with an optimal amount, promotes Development while static slack, or too little slack, promotes a Slow Rate of Learning.

Common Codes and Shared Language

In Nonaka’s view the development routines and capabilities within firms involves the aforementioned spiral of knowledge creation, where a series of conversions of tacit knowledge into explicit knowledge, explicit knowledge into tacit, and from one form of explicit or tacit knowledge to another are facilitated (Nonaka, 1991; Nonaka, 1994; Nonaka and Takeuchi, 1995). For Nonaka the driving forces for these transfers between forms of knowledge are attempts to create new knowledge and to improve the efficiency of integration of existing knowledge into the firm. Nonaka sees movements to or from tacit knowledge as involving a high degree of Social Interaction. As previously argued, this knowledge spiral is critical to the process of Development. The efficiency of the creation of new knowledge through Nonaka’s knowledge spiral is greatly effected by the extent of shared common language. It is essential that all relevant actors in the spiral share sufficient common language, such that they are able to interact with each other and thus generate new shared tacit knowledge, or convert such knowledge into an explicit form.

Within functional disciplines, geographic regions, and levels of the organisational hierarchy idiosyncratic language can develop over time. Finance departments can have one terminology when referring to the revenue performance of various products, while the marketing department can have a different terminology when discussing the same theme. Such language differences occur in the natural course of events. Common technical language can speed knowledge creation and transfer within disciplines, or managerial levels, however it may impede knowledge creation across functional boundaries. Such knowledge creation is central to the process of Development and, thus, requires the promotion of some common language across the firm as a whole.

The creation of a shared language is risky. The first risk is that it makes it much more difficult for Mavericks to operate. Shared language is a typical feature of a strong culture, which is one that resists outsiders and non-conformists. Mavericks and new comers are effectively excluded from organisation debates, or if included find difficulty in communicating their ideas to established members of the firm. The second problem which shared language can create is that of imitation. Paradoxically, whilst shared language may discourage outsiders who want to change the course of the firm, the existence of a shared language which is understood by exiting personnel will increase the firm's transparency. Thus, a strategy that is designed to promote Development and Development of current knowledge stocks may impede the process of Appropriation.

Experimentation

Authors from the literature on organisational learning and change have long argued that individuals and firms develop and extend organisational capabilities and routines through a process of experimentation (Baden-Fuller and Stopford, 1994; Huber, 1991; March, Sproull and Tamuz, 1991). Experimentation provides the firm with the opportunity to try out new ideas. The feedback provided by these experiments enables the organisation to learn via experience, thus enabling Development. Without some organisational slack the firm is so focused on production of outputs that actors have no time experiment and hence learn from experience.

Equally without a common language groups of people cannot co-ordinate their activities such that they can collectively participate in and learn from experiments. This problem is accentuated in a firm where many different idiosyncratic languages develop. In this scenario, experimentation within groups who share that common language may occur, however experimentation across groups is difficult. This impedes both Development of routines and capabilities through cross functional teams, an area which many authors argue is a key source of innovation (see Kessler and Chakrabarti, 1996 for a review of literature), and also the process of Appropriation, which by definition requires knowledge transfer across functional boundaries.

Movements Between the Processes of Use for Appropriation and Imitation (Figure Four)

There are three key forms of knowledge that flow across firm boundaries, namely, explicit knowledge (e.g. product designs), knowledge embodied in products, and knowledge embedded in the organisational routines and processes of the firm (Blackler, 1995; Geroski, 1991; Grant and Baden-Fuller, 1995; Inkpen, 1995; Teece, 1977). Migration of explicit knowledge and embodied (product) knowledge is much more rapid than embedded knowledge (Badaracco, 1991). It is not possible for the firm to halt the leakage of valuable knowledge to competitors (Geroski, 1991; Mansfield, 1985; Mansfield, Schwartz and Wagner, 1981; Ziss, 1994). An important question is how the process of Imitation by competitors is strengthened by factors internal to the firm? It is argued that changes in the levels and distribution of Codified Knowledge can stimulate *both* Appropriation and Imitation.

It is widely argued that the degree of codification of knowledge can affect the cost and ease with which it can be distributed within the firm (Nonaka and Takeuchi, 1995; Teece, 1998). Teece (1998) notes that “the more a given item of knowledge or experience has been codified, the more economically it can be transferred ... Uncodified, or tacit knowledge, on the other hand, is slow and costly to transmit. Ambiguities abound and can be overcome only when communications take place in

face-to-face situations. Errors can be corrected by a prompt use of personal feedback.” Personal feedback is costly and could act as an effective limit on the wide scale distribution of shared meanings through tacit knowledge, thus impeding maximal Use for Appropriation across the firm.

Appropriation is increasingly promoted by inter-firm alliances. Alliances can aid appropriation across a number of dimensions. First is market access and penetration (Doz and Hamel, 1998). For example in the pharmaceutical market, alliances by small firms with global firms’ enables quicker and deeper market penetration. A drug is a very knowledge intensive product. It can be the result of ten or more years of R&D (PhARMA, 1999). To maximise returns from that knowledge it is important to gain market penetration quickly and on a global scale. Global partners have distribution networks that are very costly to create. Young firms, with a limited number of drugs (often one) seek to tap into this network and share revenues with the global partner. The small firm thus appropriates a considerably larger return from its knowledge, prior to its patents running out, than if it used its limited resources to establish an independent distribution and marketing system (Ernst and Young, 1998).

Second, alliances can aid appropriation by accessing knowledge which is critical to the success of a product, but which the firm does not wish to develop internally (Grant and Baden-Fuller, 1995). Third, alliances can be used as a mechanism through which the firm allows other firms access to knowledge which it possesses but which are surplus to its requirements, in return for a fee, or knowledge exchange (Grant and Baden-Fuller, 1995). Such access could include both unabsorbed slack, such as expert advice, and absorbed slack, such as spare capacity on IT databases or R&D capabilities. Fourth, alliances can enable appropriation of a return via technology transfer. The firm transfers technology from itself to another in return for financial gain, and possibly to also control the flow of knowledge leakage from the firm into the environment (Badaracco, 1991; Teece, 1977).

In each type of alliance if, where practicable, knowledge is transferred into explicit form then the transfer costs should be lower (Teece, 1998). If the knowledge

transferred is explicit then it should also be easier for the transferring firm to legally protect that knowledge and to monitor and control the flow of knowledge across organisational boundaries. Where the knowledge transfer is tacit then the partners will need to interact directly and transfer will occur through the process of socialisation (Nonaka and Takeuchi, 1995). This may limit the viability of the alliance, due to geographic distance, scale of the knowledge transfer, or monitoring and control issues. Overcoming these problems may require the knowledge to be codified into routines. Routines can be viewed as less efficient in terms of knowledge transfer than explicit knowledge, but more efficient than tacit knowledge.

The dynamic management of codification and alliances can promote appropriation, however static management promotes imitation. Static management can be viewed as an over reliance on mechanisms to control the flow of knowledge out of the firm. These mechanisms include Intellectual Property Rights, secrecy, and casual ambiguity.

Codified knowledge is subject to imitation due to its ease of transfer, however, Mansfield (1985) found that even knowledge embedded in routines can leak out of the firm quickly. His study showed between six and eighteen months after a firm developed knowledge about new products or processes, understanding of that knowledge had leaked to competitors. This data tends to indicate that relying solely on gaining superior value added relative to competitors via *once-off* efforts to obtain greater knowledge about a product, or process, may lead to a quite short term advantage. Thus reliance on Codification as a key promoter in the process of Appropriation requires that there is a flow of new knowledge being provided by the processes of Exploration and Development.

Firms cannot necessarily rely on intellectual property rights for protection. For example, writing down knowledge in a detailed patent offers legal protection. On the other hand, given the explicit nature of a written legal procedure, patents provide other firms with a considerable insight into the nature of a product or process. They can work their way around this legal protection and imitate the product or procedure (Mansfield et al., 1981).

Avoiding intellectual property right issues by commercial secrets poses difficulties too. The problem with a commercial secret is a basic one. If a secret is shared with some one else then it's unlikely to remain a secret for long (Von Hippel, 1988). To gain maximum value, the knowledge must be leveraged across the organisation, yet this risks revealing the secret. Complex Social interactions are not limited to the boundaries of the firm. Employees have social outlets other than the firm through which knowledge may flow, including professional circles and private social networks. Modern communication technologies, and managerial systems which encourage closer interaction with actors outside the boundaries of the firm, such as just in time supply chains and inter-organisational collaborative initiatives may accelerate such interactions and, thus, diffuse key bundles of knowledge beyond firm boundaries.

The protection mechanism of casual ambiguity is a third possibility. If the actions and relationships that lead to successful completion of a set of tasks are casually ambiguous then it will be difficult for competitors to successfully imitate the capability (Peteraf, 1993), but causal ambiguity also brings risks. Collis (1994) points out that the existence of casual ambiguity in the operation of a core capability may make it difficult for firms to detect that some minor changes between resources and capabilities are destroying the core capability itself. As the complexity of a capability increases, then the likelihood of such destruction will also increase over time. Over the long term in an environment of high causal ambiguity changes to the firm's system is likely to engage in as much capability destruction as creation. The dilemma facing the organisation is to balance attempts at reducing imitation by increasing causal ambiguity with the risks of increased imitation from competitors spurred on by codification of capabilities inside the firm.

In Figure Four the engine of change, or movement between Imitation and Appropriation is Codification. It can be seen that dynamic changes in the Codification of the firm's knowledge, promotes Appropriation. Stagnation of Codification, as represented by an over reliance on the mechanisms of Intellectual Property Rights, commercial secrecy, and casual ambiguity, may encourage leakage of knowledge from

the firm to competitors and thus imitation. The feedback loop between Appropriation and Imitation indicates the negative, or antagonistic relationship that exists between each process. The negative relationship between Codification and Appropriation indicates a paradoxical relationship where Codification may simultaneously seek to make the process of Appropriation more efficient, but also promote its antagonist, Imitation.

INSERT FIGURE 4 ABOUT HERE

Complementarity and Antagonism between Characteristics

In general one can view the characteristics of Intellectual Diversity and Social Interaction as complementary. Unlearning, Mavericks and personnel turnover can all be fostered in an environment where there is a managed level of dynamic slack. With slack Mavericks can be free, within boundaries, to explore their alternative views of the firm and what its function is. Slack can also enable unlearning to occur, giving people time to develop new ways to work, without being forced to rely too heavily on the crutch of old ways that excessive pressure to deliver results in a short time period can bring. Slack may also aid in personnel turnover, enabling current staff to rotate jobs and new staff to be added. Common language may liberate people, enabling them to talk across disciplines. Unfortunately, common language may also foster an antagonism between these two characteristics. This is because it may be a cultural barrier to new personnel entering the firm. Much like an emigrant entering a country the language of which he has learned in school but never spoken amongst natives. The natives may embrace him, teaching him their colloquialisms, rejoicing in his new perspective and accent, on the other hand they may not.

There exists an antagonism between Intellectual Diversity and Social Interaction on the one hand and Codification on the other. Codification seeks to enable knowledge to flow across the organisation more quickly and uniformly, however this occurs at some compromise to the ideal of diversity. Codes require some degree of co-ordination and conformity, while diversity requires some degree of tolerance of non-conformity.

Should either mechanism meet the extreme of the other, then considerable conflict will arise. This complementary and antagonistic relationship between characteristics again has important implications for proposition three.

CONCLUSION

The main contribution of this chapter has been to review the literature on the Exploration and Exploitation dilemma and to highlight linkages across Exploration, Development and Use for Appropriation. These linkages have important implications for how knowledge Exploration and Exploitation should be managed inside firms. This chapter has pointed out that the goals of Exploration, Development and Use for Appropriation can be both complementary and also conflict with each other. Each of these processes has an antagonist. These antagonistic processes, Core Rigidities, Slow Rate of Learning and Imitation are also complementary. Finally the characteristics of the firm through which Exploration, Development and Use for Appropriation can be promoted, and their antagonistic processes suppressed, can be both complementary and in conflict with each other. Should management ignore the complementary and antagonistic relationship between each of these three groups of the system (protagonists, antagonists, and characteristics) and chose to manage Exploration, Development and Use for Appropriation as independent portfolios then the impact of difficulties in one area upon another may not be recognised. Actions to remedy problems in one area may compound problems in another. Equally inaction in one are, for example in Exploration, may have a knock on negative effect upon Development and Use for Appropriation. Delay in recognition of such inter-relationships could be potentially costly with, for example, the onset of a core rigidity reinforcing slow learning and thus impeding progress not only in Exploration but also in Development.

In reaching the above conclusion, this chapter has explored the Exploration/Exploitation dilemma in some depth, drawing upon a diverse range of literature to offer a perspective on why Exploration and Exploitation can be in conflict with each other. The processes of Exploration, Development and Use for Appropriation have also been individually discussed. An attempt has been made, drawing from the literature, to explain how each process can be promoted, or

suppressed, within the firm. These relationships are summarised in Figure Five. This figure illustrates the commonly stated dyadic relationship of Levinthal and March (1993) viewing the problem as balancing the tension between Exploration and Exploitation. As argued through out this chapter Exploitation is sub-divided into two categories, namely Development and Use for Appropriation. Thus the Exploration/Exploitation dilemma is now classified as a conflict, and co-operation, between search for and assimilation of new stocks of organisational knowledge, or *Exploration*, the expansion of current stocks of organisational knowledge, or *Development*, and the *Appropriation* of a return from stocks of knowledge accumulated through the processes of Exploration and Development. In Figure Five these processes are viewed as the protagonists in the management of organisational knowledge.

These three of protagonist processes are in an antagonistic relationship with *Core Rigidities, Slow Rate of Learning, and Imitation*. These antagonists impede outward looking absorptive capacities, descent of learning and experience curves, and inward looking absorptive capacities, which are critical to the operation of the protagonist processes. The antagonism between these processes and the protagonists is mediated by three characteristics of the firm, as outlined in section three. In Figure Five each protagonist process is exploded vertically to illustrate the intermediary role of Intellectual Diversity, Social Interaction and Codification between protagonists and antagonists. Stimulation and management of Intellectual Diversity positively affects Exploration, while its protagonist Core Rigidities, negatively effects Intellectual Diversity, thus conflicting with the process of Exploration. Stimulation and management of Social Interaction positively affects Development, while Slow Rate of Learning impedes decent of learning curves by suppressing the knowledge creation spiral of knowledge conversion as stimulated by Social Interaction. It can also be seen that Intellectual Diversity and Social Interaction are complementary, while Codification has a negative effect upon Social Interaction.

INSERT FIGURE 5 ABOUT HERE

From Figure One, and the previous discussion, it can be seen that the antagonism between Exploration, Development and Appropriation on the one hand, and Core Rigidities, Slow Rate of Learning and Imitation on the other, is complicated by the complementary nature of the antagonists, meaning that descent into one may well promote the emergence of another. Equally the complementarity and antagonism between the characteristics which trigger movement between protagonist and antagonist processes means that efforts to promote the dominance of one protagonist may trigger the decline of another. Finally, the short-term antagonism between, and the long-term complementarity of, the protagonists further complicates the management of organisational knowledge.

The principal contribution of this chapter has been to review the literature and frame diverse strands into an overall perspective as outlined in Figure Five. Both the vertical and horizontal interactions in Figure Five has been exposed and discussed at length. This synthesis of prior work characterises the management of organisational knowledge as an intensely antagonistic process. It is argued that not only are Exploration and Exploitation in conflict with each other, but that it is even difficult for organisations to sustain progress on either Exploration or Exploitation, as each has an antagonistic process which impedes it over time. This complexity challenges managers' ability to create and maintain a sustainable competitive advantage from the knowledge base of the firm, and yet this is one of the key propositions of the Knowledge Based View of the Firm.

The remaining chapters of this thesis seek to explore a number of questions that arise from this review. In Chapter Three, an in-depth case study is analysed to explore whether Exploration and Exploitation can be measured in a real organisational context. An analysis of the Celltech case casts light on proposition one of this chapter. It can be seen from this analysis that Exploitation can be sub-divided into Development and Use for Appropriation. All three concepts can be separately identified inside Celltech and measures of each are observed. The Celltech case also casts light on proposition four. It is found that balance between Exploration and Exploitation did not always exist inside this firm, but that for a period of half a decade balance was maintained. Chapter

Three seeks to find evidence as to whether a real firm can experience the tension within and between the processes of Exploration and Exploitation and how these are managed. This casts light upon proposition three. In the fourth chapter the important question of whether shareholders attach value to the outputs of Exploration and or Exploitation (Development and Use for Appropriation). If so what value is generally attached to each activity and is there empirical support for the contention by Levinthal and March (1993) that Exploitation activities are rewarded with greater financial returns. This casts light upon proposition two, observing that both Exploration and Exploitation activities are valued by shareholders.

FIGURE ONE: BALANCING THE EXPLORATION/EXPLOITATION DILEMMA AS A TRIAD OF ANTAGONISTIC PROCESSES

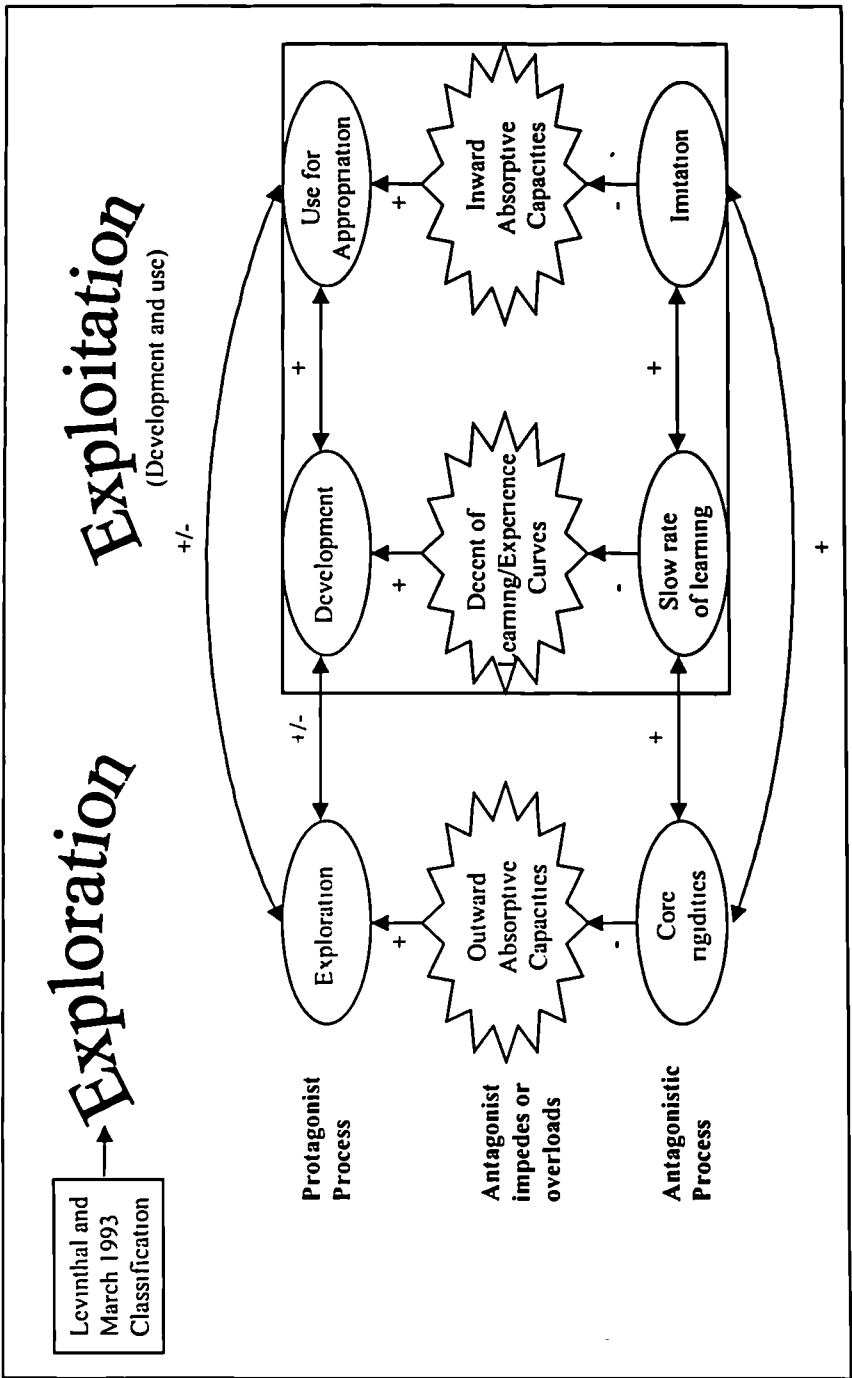
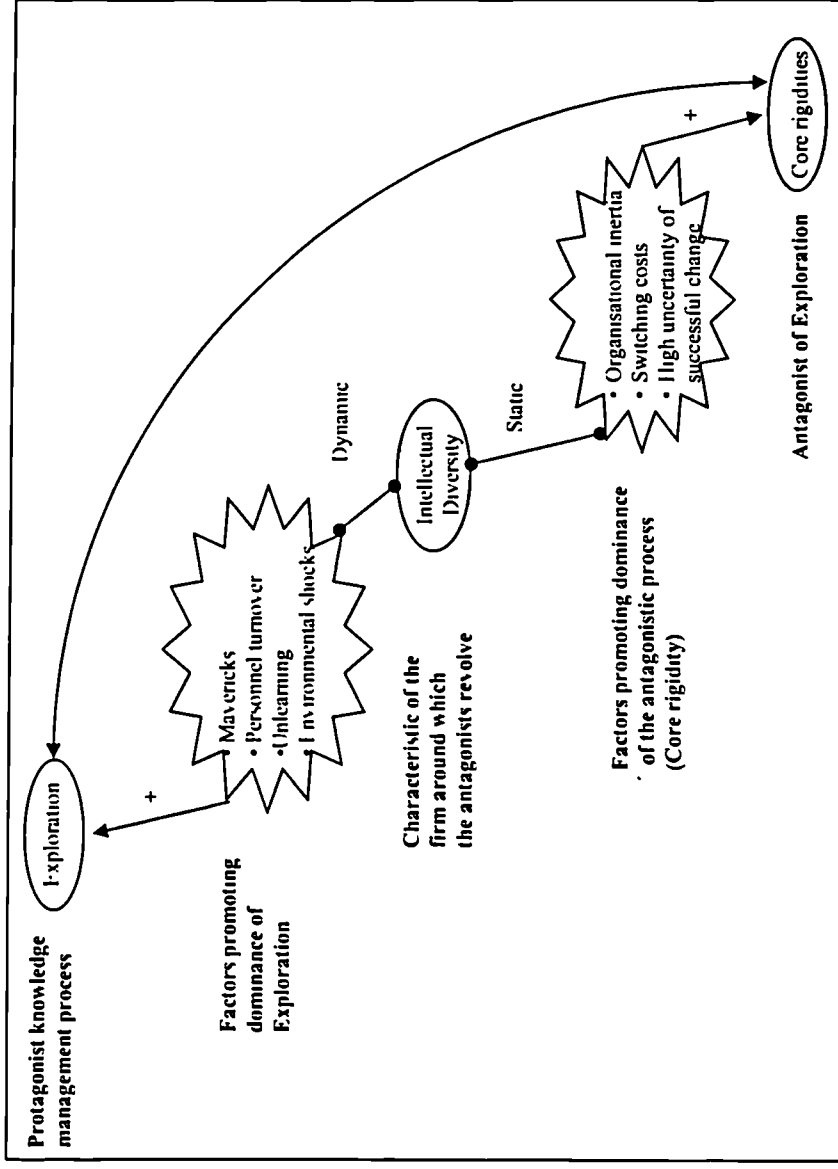
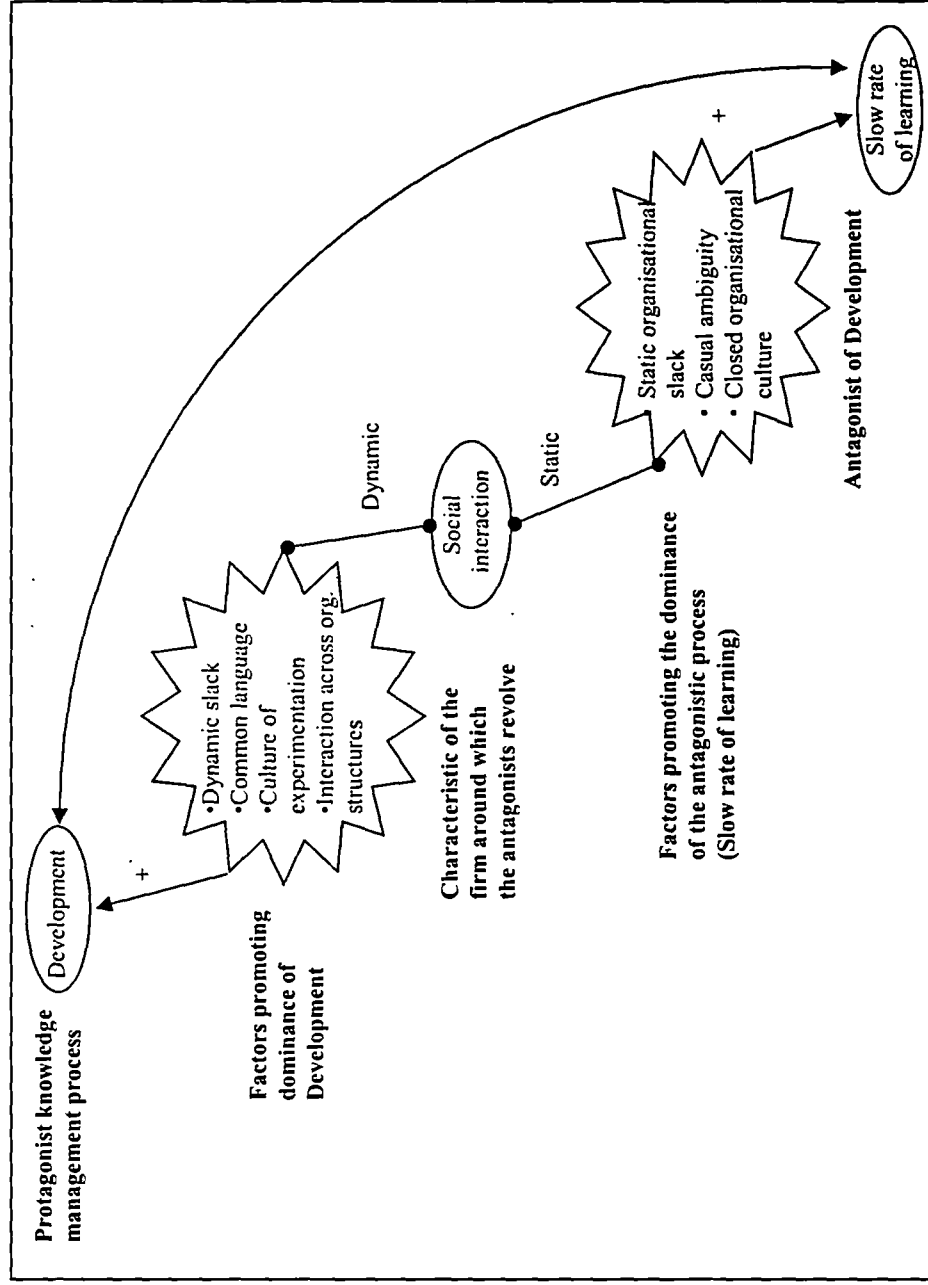


FIGURE TWO: THE ANTAGONISTIC NATURE OF KNOWLEDGE EXPLORATION



Note: + indicates a complementary, or reinforcing relationship
 - indicates an antagonistic relationship

FIGURE THREE: THE ANTAGONISTIC NATURE OF KNOWLEDGE DEVELOPMENT



Note: + indicates a complementary, or reinforcing relationship
 - indicates an antagonistic relationship

FIGURE FOUR: THE ANTAGONISTIC NATURE OF APPROPRIATING A RETURN FROM KNOWLEDGE

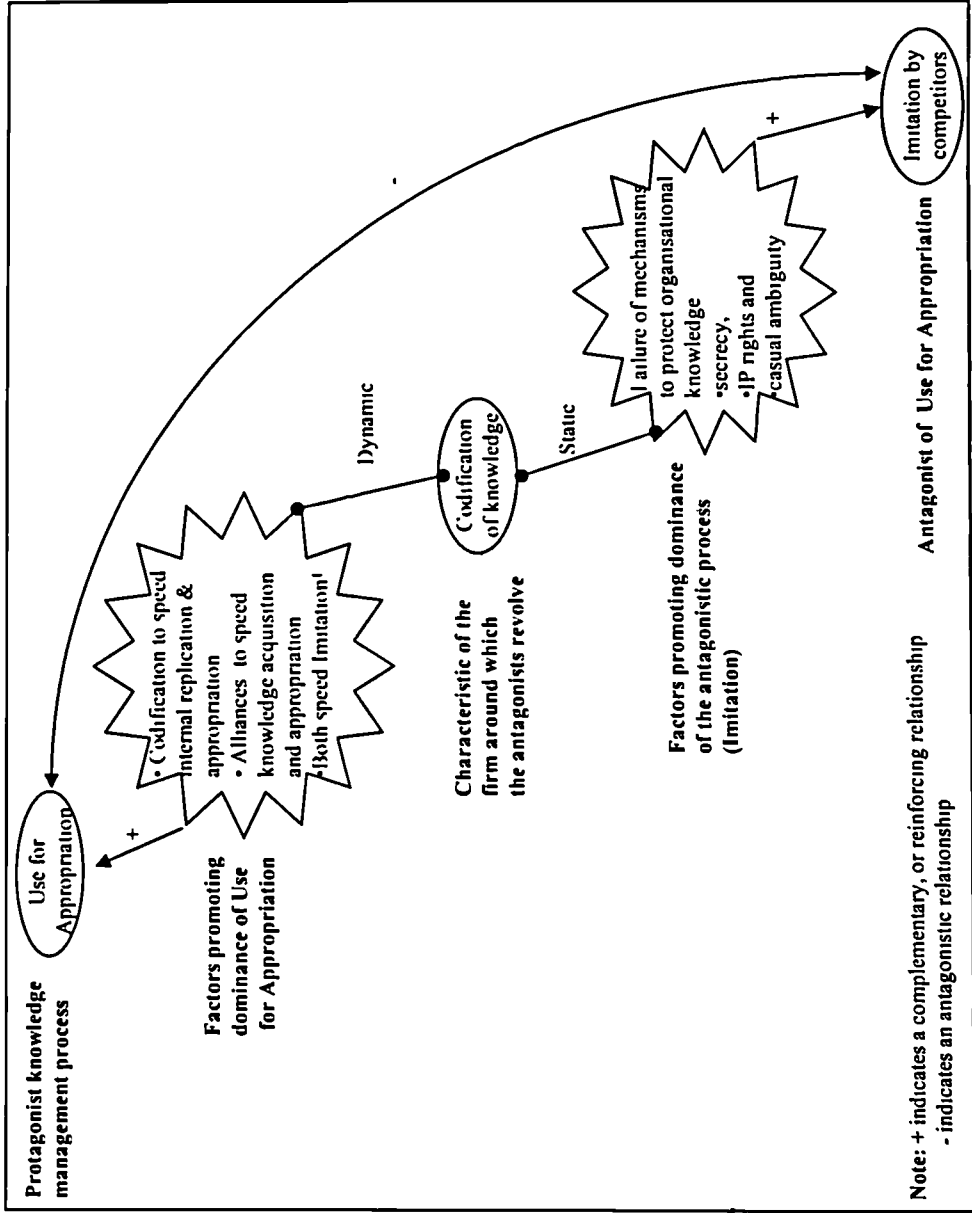
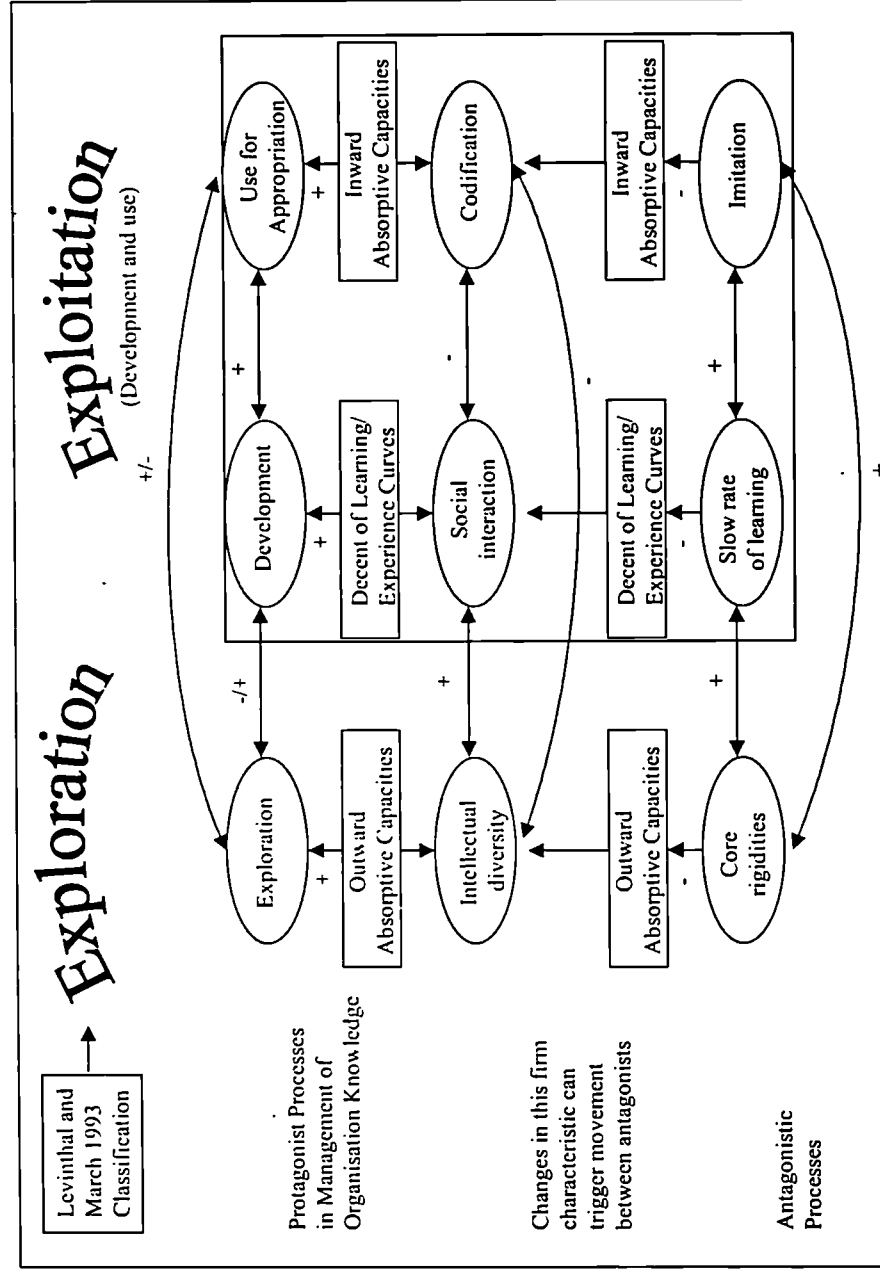


FIGURE FIVE: AN ANTAGONISTIC SYSTEM OF KNOWLEDGE MANAGEMENT



Chapter Three:

Balancing Knowledge Exploration and Exploitation in a Real Organisation Over Time:

Lessons from the Celltech Case

INTRODUCTION

In the previous chapter the Exploration/Exploitation dilemma and the maintenance of balance was explored. This chapter studies the management of Exploration and Exploitation (Development and Use for Appropriation) inside the oldest biotechnology firm in the UK, Celltech. The Celltech case study is provided in full in the appendices of this thesis. In this chapter it will be shown how Celltech moved from a situation in which Exploitation had come to dominate over Exploration, in a manner much as predicted by Levinthal and March (1993). The greater short-term financial rewards of investments in Exploitation activities came to drive out investment in Exploration. The analysis of this case shows how Celltech moved away from a dominance of Exploitation activities, reinvested in Exploration, and installed administrative systems to aid maintenance of a balance between Exploration and Exploitation activities. The analysis of Celltech both demonstrates that within a real organisation the balance of Exploration and Exploitation is a real issue for firms seeking to manage their stocks of organisational knowledge and also offers insights into how movement between Exploitation and Exploration can be managed and balance maintained over time.

The Celltech case occurs in the context of organisational renewal, having experienced a decline in the late 1980s followed by turnaround and renewal in the 1990s. The management of investments in Exploration and Exploitation (Development and Use for Appropriation) were an important feature of this story of decline and rejuvenation. The theoretical issues raised in the previous chapter provide an important frame of reference in the analysis of the Celltech case, however a short additional theoretical

review needs to be added at this stage, namely, the role of Exploration and Exploitation in the context of organisational renewal. To this end this chapter begins with a short theoretical section on renewal and the Exploration/Exploitation dilemma. In the second section of this chapter the methodology employed to create the Celltech case is briefly outlined. In the third section an overview of the Celltech case is provided. This provides important information on Celltech's organisational context. In the third section Celltech's renewal is explained by applying the lens of Exploration/Exploitation. The fourth section details the organisational tools that Celltech employed to move from an imbalance favouring Exploitation to renewal through Exploration, eliminating Core Rigidities, and the installation of systems to maintain a balance between Exploration and Exploitation. The fifth section offers some lessons from the Celltech case. The final section links the analysis of Celltech back to the theoretical chapter. It is observed that that the Celltech case exhibited much of the factors promoting the dominance of Core Rigidities and Slow Rate of Learning outlined in figures two and three of the previous chapter, while the changes instigated between 1990 and 1998 involved pulling many of the levers outlined in those figures that promote the dominance of Exploration and Development (Exploitation).

THEORY

As outlined in Chapter Two, it is widely argued in the literature that a central component of success is the maintenance of a balance of *Exploration* and *Exploitation* (*development and Use for Appropriation*) within the firm (Cohen and Levinthal, 1990; Levinthal, 1997; Levinthal and March, 1993; Hendry, 1996). In common with others, March (1991) observed that the maintenance of a balance between Exploration and Exploitation is "a primary factor in system survival and prosperity." Celltech's story, elaborated below, runs counter to the oft stated theoretic proposition in the literature that Exploitation tends to dominate over Exploration. This logic is summed up by Levinthal and March (1993):

"Exploitation generates clearer, earlier and closer feedback than Exploration. It corrects itself sooner and yields more positive returns in the near term. As a result, the primary challenge to sustaining an optimal mix of Exploration

and Exploitation is the tendency of rapid learners and successful organisations to reduce the resources allocated to Exploration.”

In mature organisations Exploitation tends to drive out Exploration, making renewal based on Exploration very difficult. Renewal based on the creation and application of new core capabilities is very difficult (Leonard-Barton, 1995; Peteraf, 1993). The key problem is that the development of core capabilities tends to be path-dependent (Cohen and Levinthal, 1989; 1990; 1994; Collis, 1991; Mahoney, 1995). The initial success of a core capability leads to its growth over time. Success based on the Exploitation of that core capability reinforces the behaviours upon which it is based. Over time these behaviours become deeply embedded in the organisation. This process of development (or deepening) of a core capability enables the firm to refine its organisational routines and procedures in knowledge integration to such a point that it knows more than any other firm about how to deliver, efficiently and effectively, value added to a particular market. But as market needs change over time, other knowledge bases may emerge to deliver superior value added. This shift may ‘maroon’ established ‘mature’ firms, leaving them with core capabilities that are no longer appropriate (Herriott, Levinthal and March, 1985; Miller, 1993). The resulting rigidities are due to the high switching costs involved in changing core capabilities (Kogut and Zander, 1992); inertia within the organisation (Huff, Huff and Thomas, 1992); and the high level of uncertainty (and hence cost) attached to investments in the Exploration of new knowledge (Levinthal and March, 1993; March, 1991).

As the firm hits a performance crisis the natural predisposition of employees is to get out of trouble by focusing on doing what they currently do more efficiently. They rely on the core competencies of the past to deliver success once more. Efficiency drives enable the firm to avoid confronting the very difficult realisation that its past core competencies are now Core Rigidities and must be replaced, rather than overhauled. It is very difficult for organisational members to abandon past successful behaviours and explore new knowledge upon which to create new core competencies that better meet the needs of the market.

There is, of course, a literature on corporate restructuring and renewal. The restructuring strand is typically understood as refocusing through downsizing of a business unit or the shedding of unprofitable units from a multi-unit firm (Hoskisson and Hitt, 1994; Markides, 1995; Robbins and Pearce, 1992). Celltech had only two divisions, reducing the relevance of these proscriptions. Moreover, its renewal was based on revitalising the smaller, unprofitable research division not the profitable contract division. The literature on business renewal is more relevant, for it argues that in exceptional circumstances defunct firms or businesses can rejuvenate (Baden-Fuller and Stopford, 1994; Grinyer, Mayes and Mc Kiernan, 1988; Pettigrew and Whipp, 1991). Until now, much of the evidence has come from the so-called mature sectors, and the relevance to high technology sectors has yet to be established. For high technology firms, such as those in biotechnology, there are serious technical issues to be confronted. Given the hyper-competitive nature of the environment (D'Aveni, 1994), the paradigmatic shifts in technology (Powell, Koput and Smith-Doerr, 1996) and the need for fast strategic moves (Brown and Eisenhardt, 1997), a serious question arises as to whether any renewal is possible and, if it is possible, whether the models of renewal in maturity are relevant.

The story of Celltech is unusual on two levels. First, it is an example of a mature high technology firm successfully engaging in renewal. Second, this renewal was focused around a strategy that enabled the firm to escape the gravity of Exploitation and move towards a model of financially successful Exploration. Its renewal is particularly unusual in that shareholder value rose after renewal from near bankruptcy and illiquid stock in 1990 to a publicly traded firm with a market capitalisation of \$ 502 million by 1999 (Mc Namara, 1999) and £ 1,081 million by January 2000. This rise in shareholder value occurred in spite of the fact that prior to the change in 1990 the firm had been marginally profitable, and from 1990 to 1998 it has posted cumulative net losses of £75.9 million.

METHODS AND DATA COLLECTION

Sources of Data, Validity and Reliability

The validity of the case study was maintained through rigorous data collection. The first source of data was five interviews with senior executives inside the case company, and the analysis of extensive relevant company documents on investment, revenues, new product development, clinical trials, and alliances. The second was a search of public domain data on all independent drug biotechnology firms listed on the London Stock Exchange, which included Celltech. The third source of data was a series of case studies, interviews with executives from other biotechnology companies and interviews with executives from the London Stock Exchange, which helped to check the interpretation of both the sector and the firm. In common with other case study research, a central output of the data collection and analysis process was the writing up of a detailed case study (Eisenhardt, 1989). The written up Celltech case study is provided in full in the appendices. Another two supporting case studies, PolyMASC and Oxford Molecular are also provided in full in the appendices. To ensure that the researcher's understanding of the industrial context was valid a companion document on the biotechnology sector was written. This paper provided a statement of what the biotechnology sector is and the nature of competition within it. This paper was first reviewed by the Professor of Chemical Engineering to ensure accuracy, and was modified to incorporate his expert comments. The note on the UK biotechnology sector was then submitted to the Celltech management for review and was approved by them as a valid overview of the sector. This document was some 25 pages in length in single line spacing and given its background nature is not included in the appendices. Triangulation of data sources helped to ensure validity (Jick, 1979; Kirk and Miller, 1986). For all three cases respondent validation was employed, where executives from the organisation commented on drafts of the case (Silverman, 1993; Whyte, 1984). Through a process of iterative rewrites, the final cases sought to incorporate a shared understanding by both the researcher and the executives of the firm's story.

The executives in Celltech were keen to explain the competencies they had created and the dilemmas they faced. Being scientists they were highly articulate, meticulous about the data in support of their claims and able to point out sources of data which allowed Exploration of the phenomena under discussion in this chapter. As such the interviews proved to be an excellent source of data and, despite the small number, showed a surprising degree of agreement and comprehensiveness. No indication was found that further interviews among seniors or juniors would reveal any significant new insights. To protect the reliability of the study a chain of evidence was created and maintained throughout the process (Yin, 1989). All interviews were transcribed.

Public documents were searched in a methodical manner. The annual reports from 1987 to 1998 were obtained for Celltech and carefully analysed. Annual reports for all other biotechnology firms listed on the London Stock Exchange were also obtained to gain a familiarity with the competitive dynamics of the sector. Background information on Celltech and other UK biotechnology firms was obtained by a search of the general news media since the early 1990s. This was done using a combination of the CD-ROM database McCarthy and the on-line database Reuters Business Briefings, both of which contain much of the UK's leading news media sources. Much of this data is subsequently analysed in some depth in Chapter Four of this thesis in an event study that empirically observes the shareholder wealth creation effects of announcements about Exploration, Development and Use for Appropriation. Additional general data on the biotechnology industry was obtained by a search of the Economist CD-ROM from 1987 to 1996, the Ernst and Young European Life Sciences report 1998, reviews of *Genetic Engineering News* and *Pharmaceutical Business News*, both leading industry magazines, and the web-sites of biotechnology and pharmaceutical industry associations and firms.

The interview process

Understanding the processes of knowledge management and renewal in a high technology firm presents technical challenges to management researchers. Thus the interviews of Celltech executives were conducted with a Professor of Chemical

Engineering present, who has experience of technical research in the field. His knowledge of the science was essential in understanding the nuances of the business and relating these to the managerial processes explored in this article.

Five managers were interviewed from differing levels in the organisation. These were the Chief Executive of the group, the Director of Finance, the Chief Executive of the Therapeutics division, the Director of Research, and the Director of Development. Both the Directors of Development and Research were involved in a hands-on way with actual projects, having been Celltech project leaders in the 1980s and early 1990s. All except the Finance Director have PhDs in science and have previously worked for many years in the pharmaceutical sector. These five executives were pivotal in the reorientation of Celltech's strategy in the 1990s. The group Chief Executive was interviewed first, following a broad interview schedule. This interview fleshed out the overall picture and a new set of interview questions was developed for the remaining four interviews. During early interviews issues arose which were unexpected, to which follow up questions were applied both within and across interviews. By the end of the five interviews, the interviewers felt that they had obtained an understanding of the firm. The last interview did not reveal any significant new information, rather it provided triangulation of existing data.

The focus of interviews was initially upon one successful innovative drug R&D project. This project, known as CDP 571, which had been identified as critical to the success of Celltech by the Professor of Chemical Engineering, and was confirmed as such by each of the interviewees. From this core focus executives detailed not only their experience of managing this critical project, but in turn the wider management of Celltech as a firm that encompasses a diverse range of drug discovery and development projects. A drug R&D programme such as CDP-571, which sought to develop a cure for Septic Shock, involves two broad types of task. The first is drug discovery, where compounds are identified, or generated, and shown to have potential as a drug. The second task involves going through a series of three, or more, clinical trials where it is proved to regulators that the drug is both safe for public use and is of clear therapeutic benefit. Such projects encompass both elements of Exploration for

new knowledge, Development of current organisational knowledge, and the Appropriation of a return from the process of knowledge creation and use.

Classification of activities as Exploration and Exploitation

Based on the three case studies, and background research on therapeutic drug discovery and development in the biotechnology sector, it became clear that three activities are of key importance to the success of firms and executives within the sector. First is the discovery of novel drug compounds. The process of drug discovery involves the search for novel compounds that may have therapeutic benefit. The goal is to identify, or construct, a promising compound that can be patented. Pre-clinical trials are conducted on the compound, often involving experimentation on animals, to determine if the drug has both a therapeutic function, in other words that it can tackle a given disease or illness, and is not so toxic to the recipient as to cause more harm than benefit. Especially in the Oxford Molecular case study it can be seen that the discovery process involves a high degree of search for and creation of new knowledge. It is a highly uncertain process, with less than 5 in 5,000 compounds identified in the discovery process actually making it through to the next stage, clinical trials on humans (Berry, 1996; PhARMA, 1999). At the heart of a drug discovery process is the attempt to create new stocks of organisational knowledge and embed these in a patented compound that can be later subjected to development via human clinical trials. Thus drug discovery in this thesis is classified as an Exploration activity.

The second task that was identified as being of critical importance to the success in the case companies was the development of a drug through a series of human clinical trials to gain regulatory marketing approval of the drug. Once a compound has completed pre-clinical trials it can seek entry to human clinical trials. These clinical trials normally consist of three main types referred to as Phase I, Phase II and Phase III clinical trials. Phase IV trials, once marketing approval has been obtained are increasingly undertaken, though these were not undertaken by any of the case companies or the sample in the event study and are hence not discussed in this thesis. Phase I clinical trials study the effects of the drug on a small number of volunteers to

establish its safety. Despite the long experience of the pharmaceutical industry in drug discovery and development the move from pre-clinical trials on animals to clinical trials on man is still an uncertain process. Despite pre-clinical data and extensive molecular modelling one cannot be sure of the effect that a compound will have upon man. Thus the process of Phase I trials is essentially one of Exploration. The researchers are seeking to establish the safety and effects of the compound in a new environment, man.

Upon successful completion of Phase I trials, Phase II clinical trials can be undertaken to test if the drug is of therapeutic benefit, that is does it result in an improvement in the patient's condition. It also tests the range of dosages and their effects. Phase II trials often test the effectiveness of the drug in tackling a condition relative to a placebo group, and also test a range of tolerable doses to determine the most effective dose. Essentially Phase II trials involve an incremental extension of the firm's stock of knowledge about a drug. Pre-clinical trials have identified the drug and Phase I trials explored its application in man. Thus Phase II trials can be viewed as being Development of current knowledge.

Phase III clinical trials seek to establish whether the drug has a clear clinical benefit relative to another drug on the market place, or the standard treatment. If the drug passes Phase III trials then the firm can seek a Product License Application (or equivalent). If regulatory authorities are convinced by the power of the clinical trial data contained in the Product License Application then it may be approved for marketing as either a prescription or over the counter drug. Phase III trials are essentially a further incremental development of the firm's stock of knowledge and are thus classified as Development.

The third area of value creation that managers consistently mentioned was the formation and management of alliances. Executives from the three case companies argued that alliances with both pharmaceutical and fellow biotechnology companies form a central aspect of successful competition in the biotechnology sector. This view is supported by empirical studies of the sector in the strategy literature (Hagedoorn,

1993; Powell et al., 1996; Stuart, Hoang and Hybels, 1999). Managers noted that alliances serve four main purposes. First, alliances often bring access to financial resources. In each of the three case studies in the appendices the firm was many years away from net profit based on sales of final products. In the interim period operations are primarily funded by payments from alliance partners and equity. This view of alliances can be classified Exploitation, or as Use for Appropriation. Biotechnology firms share their portfolio of patented compounds and drug discovery capabilities with partners in return for cash payments, thus appropriating a return from their current stock of organisational knowledge. Alliances can also be viewed as involving Use for Appropriation where the purpose of the alliance is to combine an approved drug with a pharmaceutical firm's marketing capabilities to maximise sales in the final market.

Second, managers viewed alliances as offering signals to shareholders as to the worth of their current stocks of knowledge. The logic expressed was that if major alliance partners are willing to invest their scientific reputations by collaborating on a specific drug discovery or development project then the current knowledge stocks of the biotechnology firm must be valuable. Managers believed that such validation raised the value of their firm's stocks making access to capital markets for further funds easier. In this context alliances can be viewed as Exploitation, or Use for Appropriation. The goal is to raise stock price to enable access to capital markets. Essentially the firm trades its current stock of knowledge with an alliance partner in return for which it receives scientific and commercial validation, which raises the value of the firm's knowledge stocks in the eyes of the shareholder. The Celltech experience, outlined in Appendix One, demonstrates that such validation aids a return to the capital markets.

Third, managers viewed alliances with major pharmaceutical firms as offering access to complex drug development capabilities. The capabilities of the three case companies in the appendices were primarily in drug discovery, yet for a drug to make it to the market they need to pass through complex regulatory clinical trials. Pharmaceutical firms have formidable capabilities in the management of clinical trials. In this view alliances can be seen as primarily about development of the biotechnology firm's

current stock of knowledge. The biotechnology firm often takes the drug through Phase I clinical trials. It then seeks a partnership with a pharmaceutical firm to facilitate the incremental development of the knowledge created through the biotechnology firm's drug discovery and Phase I clinical trial capabilities by accessing the pharmaceutical firm's capabilities in Phase II and III clinical trials. Such combination is not a simple process. It requires the combination of knowledge from both the pharmaceutical and biotechnology company if successful Phase II and III clinical trials are to be constructed and implemented. Unlike the case of a marketing alliance, where interaction might well be minimal, it can be seen from the example of Celltech's alliance with Bayer that interaction and knowledge combination is required in co-development of a drug. In this view alliances can be seen as being about Exploitation of knowledge via the process of joint Development of two firms current stocks of knowledge.

Fourth, managers viewed alliances as offering learning benefits. Alliances were used by Celltech to learn how to manage human clinical trials, thus creating a new stock of organisational knowledge in the area of drug development. In this context alliances can be viewed as being about Exploration for new organisational knowledge. It should be noted that managers often believed that over the life span of an alliance it could achieve all four goals, thus a single alliance could contain elements of Exploitation (both Development and Use for Appropriation) and Exploration.

From the above it is argued that alliances in UK therapeutic biotechnology firms can be argued to contain information on the full spectrum of Exploration/Exploitation. Alliance formation and participation may facilitate Exploration for new stocks of organisational knowledge, Development of current stocks of knowledge, and Appropriation of a financial return from organisational knowledge creation and development activities.

AN OVERVIEW OF CELLTECH

Celltech can be viewed as having four basic historical periods, which link to the balance of the Exploration and Exploitation of knowledge. For the first decade of its

existence, two separate strands of the business were grown: contract manufacturing and research (Biologics) and in-house research and development (Therapeutics). The goal was to cover the costs of in-house R & D with revenues generated by doing contract research on behalf of other firms. From Figure One it can be seen that after an initial period in which R & D expenditure exceeded Biologics turnover, by 1985 R & D amounted to less than 50 per cent of turnover, and by 1987 this was at an all time low of 25.5 per cent, recovering to 50 per cent by 1990.³² In 1987 there were marginally more employees located in the Therapeutics division than in Biologics. By 1990 the number of staff located in the Biologics contract research and manufacturing business was at an all time high of 60 per cent. Hence this time frame is referred to as the Biologics period. During this period the firm developed strong technical capabilities (Dodgson, 1991), although executives interviewed as part of this thesis commented that the firm was consequently very hierarchical and lacked capabilities in interdisciplinary research that were necessary for success in the discovery and development of innovative drugs.

INSERT FIGURE ONE ABOUT HERE

In the second period (1990 to 1992), a new CEO joined the firm with a new perspective. He saw the future as being in the development of innovative new drugs in which Celltech had a slice of the action. As he puts it, “the winners have to be the companies that are therapeutic because the value added is so huge.” The firm was *formally* split into two divisions, Biologics and Therapeutics, and the CEO implemented his new strategic vision by expanding the Therapeutics division. From Figure One it can be seen that this expansion resulted in an increase in the amount of inputs devoted to Therapeutics. The percentage of turnover devoted to own R & D and the number of employees in the Therapeutics division both rose sharply. Within this division the firm developed a capability in the creation of innovative drugs from initial discovery through to regulatory clinical trials. This change in strategy required a shift

³² Data on turnover and R & D are only available from 1983 onwards. Data on the split of employees by division were not available prior to 1987.

away from core capabilities centred around technology application and towards interdisciplinary research to create new drugs as opposed to new technologies. Thus this period is referred to as re-asserting R & D, where the role of R & D was accentuated, while the role of contract manufacturing and research, in terms of number of employees and turnover, was marginally reduced (see Figures 1 and 2).

In 1992 the third period began which lasted until 1996. From Figure One it can be seen that during this period the inputs devoted to Biologics and Therapeutics were largely in balance. The firm developed a strategy of collaboration with large pharmaceutical firms in the development of its drugs. This time frame is referred to as the alliance period. The benefits of such collaboration was outlined by the firm as follows:

“They bring extensive expertise to the planning and conduct of clinical trials in order to seek registration for products in a timely manner. They have marketing expertise and strength in the therapeutic areas that should allow them to optimise the launch and market penetration of new products... Collaborative agreements also demonstrate third party validation of the scientific and commercial potential of innovative discovery or development programmes.” (1996 Annual Report)

Current collaborators include some of the leading pharmaceutical firms in the USA and the EU. The quality of Celltech’s collaborators and the number of drugs it has in both clinical trials and in discovery projects compares favourably with its major biotechnology rivals. This collaborative strategy enables Celltech to exploit its knowledge base before going to the end market, via cash milestone payments from collaborators, but without selling a full interest in the downstream property rights. Milestone payments and collaboration are not unusual in this sector. Celltech was, however, amongst the first in the UK to successfully implement this strategy. It is also unusual in the breadth and quality of its collaborators.

The fourth period began in 1996 when the Biologics division was sold for £50 million, thus this period is referred to as the post-Biologics era. This signalled the final stage of

Celltech's new direction. In 1990 Biologics dominated the firm to the detriment of R & D. With the sale of Biologics Celltech had in six years converted itself into a firm solely focused on the R & D of innovative drugs to the exclusion of contract manufacturing and research. From Figure One it can be seen that all inputs are now focused on own R & D. The value of the firm has see-sawed over its life. From near bankruptcy in 1990, Celltech had been transformed. By 1998 it had a market capitalisation of around \$502 million. An analysis of stock market performance shows that Celltech ranked eighth out of 50 independent European biotechnology firms, having experienced a 25 per cent increase in share price in 1998 (Mc Namara, 1999). This renewal occurred not by intensifying the firm's focus on the Exploitation of organisational knowledge, but rather by refocusing on Exploration.

EXPLORATION/EXPLOITATION AS A LENS IN UNDERSTANDING CELLTECH'S RENEWAL

This transformation from Biologics to Therapeutics can be explained in terms of the Exploration/Exploitation balance. Investment in Biologics can be viewed as essentially being an investment in Exploitation (Development and Use for Appropriation). Celltech had developed world-class technical capabilities that leveraged the firm's knowledge of antibodies and recombinant DNA through contracted manufacturing. Such contract manufacturing was is a good example of Exploitation of a current stock of knowledge by incremental development of antibody production capabilities, while appropriating a return from this stock of knowledge via contract manufacturing. Incremental development of these capabilities did occur, but only in the context of learning by doing in the contract research division. Investment in contract manufacturing had a rapid feedback from the market in terms of contracted revenues.

Celltech's investment in Therapeutics can be viewed as knowledge Exploration in Levinthal and March's (1993) terms where Exploration is "the pursuit of new knowledge of things that might come to be known." Drug discovery requires that knowledge from multiple technical disciplines (for instance, molecular biology and medicinal chemistry) be combined in the creation of an innovative compound that can enter clinical trials. In 1990 this Exploration became more intense as the firm sought to

develop its capabilities in interdisciplinary drug discovery. The feedback from the market is not as clear, nor as fast, as in the case of Biologics' contracts. As observed from Table One of Chapter One, the discovery of a compound takes on average 6 years, though in many cases considerably longer; the drug development process is estimated to take a further 8.9 years on average (PhARMA, 1999). As noted in the methodology section, only 5 in 5,000 compounds that enter discovery programmes are estimated to make it to developmental clinical trials, and only one of these to make it on to the market (Berry, 1996; PhARMA, 1999). The cost of taking a drug through this process is estimated to be in the region of \$300–\$500 million (BIO, 1996).

INSERT FIGURE TWO ABOUT HERE

From Figure Two it can be seen that Celltech was experiencing very considerable growth in Biologics turnover from 1987 to 1989. Gross margins attributed to the Biologics activity, while falling, were quite high, ranging from over 31 per cent to 12.5 per cent. On the back of Biologics' success the firm was able to invest £17.3 million in Therapeutics R & D during this period, while also generating a net profit of £900,000. Therapeutics was not generating any turnover during this period. In this context one can see that for a firm such as Celltech in the 1980s, the temptation to focus resources on Exploitation rather than Exploration was very real.

The balance between Exploration and Exploitation in Celltech can be seen from two perspectives: allocation of resources to each activity (Figure One) and revenues generated (Figure Three). As noted earlier, from Figure One it can be seen that from 1985 to 1990 investment in Celltech's own R & D as a percentage of group turnover initially declined, and remained below 32 per cent until 1990, when it dramatically increased to 49 per cent with the arrival of the new management team. The number of employees working in the Therapeutics division declined over the period from 1987 to 1990. Employee numbers is a key metric as both R & D and contract manufacturing and research are knowledge and labour intensive activities.

In addition to a rising commitment to Biologics in terms of inputs, as seen in Figure One, there was a parallel rise in level of turnover, or outputs, that Biologics generated (see Figure Three). Combining Figures One and Two it can be seen that during the period from 1985 to 1990 Exploitation (Biologics) came to dominate over Exploration (Therapeutics).

INSERT FIGURE THREE ABOUT HERE

The re-asserting R & D period from 1990 to 1992 can be seen in Figure One in terms of a sustained rise in the percentage of employees located in Therapeutics. New employees were hired within Therapeutics while there were redundancies within Biologics. Figure Three indicates that in terms of one simple output measure, turnover, the Therapeutics division was also beginning to make an impact. Retrenchment in the Biologics division can be seen in Figure Three in terms of a decline in turnover generated by the division. Thus it can be seen that the imbalance between Biologics and Therapeutics in terms of resource inputs and revenue outputs began to be reversed.

The alliance period represents a time of sustained balance between the inputs allocated to both Exploration (Therapeutics) and Exploitation (Biologics). From Figure One it can be seen that the number of employees located in each division is largely in balance. From Figure Two it can be seen that the performance in Biologics in terms of margins improved over the period. From Figure Three it can be seen that both divisions experienced a rise in revenues up to 1995, and a proportional decline in 1996. Thus over a period of half a decade, from 1992 to 1996, Exploration and Exploitation in terms of inputs (Figure One) and outputs (Figures Two and Three) were largely in balance.

Exploration/Exploitation inside Therapeutics

At the start of the fourth period, in 1996, the Biologics division was sold off. By that time Therapeutics had developed its own sophisticated balance of Exploration and Exploitation dimensions. All three Exploration activities defined in the methodology

section are observed in the Therapeutics Division, namely, discovery of new drugs; Phase I clinical trials; and development of a capability in collaboration with large firms. Exploration within this division can be seen in its purest form as the discovery of new drugs. Drug discovery by its very nature involves “the pursuit of new knowledge of things that might come to be known” (Levinthal and March, 1993). The objective is the discovery of a new innovative compound which tackles an illness that currently lacks a drug therapy, or a compound that is based on a sufficiently novel combination of knowledge that it does not violate current patented compounds. From Figure Four³³ it can be seen that from 1990 to 1998 Celltech has considerably increased the number of identified discovery projects.

INSERT FIGURE FOUR ABOUT HERE

As noted in the methodology section Phase I trials are classified as an Exploration activity and the number of such trials is found to have varied over time inside Therapeutics. These trials represent about 11 per cent of the cost of performing clinical trials (Parexel International, 1996). From Figure Four it can be seen that this form of Exploration peaked during the period of balance between 1992 and 1996, and that a reduction in Phase I trials during 1997 and 1998 has been offset, in exploratory terms, by a rise in the number of identified discovery projects.

The third form of Exploration noted in the methodology is the creation of the capability to collaborate with large pharmaceutical firms. By 1990 two drugs were in clinical trials, and the number has risen dramatically since then (see Figure Four). This has been achieved by accessing the drug development capabilities of large pharmaceutical partners through collaboration, with the partner taking the lead in the management of clinical trials. Through interaction with pharmaceutical partners on development projects, Celltech has, according to executives within the firm, developed a capability in managing collaborations with large firms. Such collaborative capabilities are argued in the literature to be a powerful source of competitive

³³ Data on the number of drugs in clinical trials were not available prior to 1987.

advantage in general (Gulati, 1999). Within the biotechnology sector collaborative networks, and the ability to work within them, is found to be a central source of innovation and value creation (Powell et al., 1996; Shan, Walker and Kogut, 1994). The initial development of this capability can be viewed as another example of Exploration.

In the methodology section of this chapter two main forms of Exploitation were identified that are observed in the Therapeutics divisions, namely Development, as represented by Phase II and III clinical trials and appropriation, as represented by alliances. Phase II and III trials are essentially Development of current stocks of knowledge, as embedded in the compound, rather than classic Exploration. Phase II trials represent about 27 per cent and Phase III trials about 62 per cent of the costs of the clinical trial process (Parexel International, 1996). From Figure Four it can be seen that the number of Phase II and III clinical trials increased marginally in the period of re-asserting R & D (1990 to 1992), while in the alliance period (1992 to 1996) there was both an increase (in 1993) and a slight decline (in 1996). In the post-Biologics era there has been an increase in the number of drugs in Phase II trials, representing an increasing focus on Exploitation.

The second form of Exploitation is the management of prestige alliances³⁴. Prestige alliances can be viewed as *predominately* exploitative. All four forms of Exploitation through alliances identified in the methodology section are observed in the Therapeutics division. First, alliance partners provide milestone payments to Celltech for achieving prescribed stages in the discovery and development of a drug. Between 1992 and 1998 out of a potential £83 million a total of £26.5 million in milestone payments was made to the Therapeutics division by collaborators. Second, prestige alliances enable Celltech to access world-class drug development and marketing capabilities, which enhances the value of their drug portfolio. This access is critical to the development of the knowledge embedded in the discovered compound. Celltech

³⁴ Alliance partners are classified as prestige if they are in the top 20 firms in terms of pharmaceutical turnover as compiled by IMS Health and listed in Firm, 1999.

had little development experience in 1990, and no experience of the world-wide marketing and distribution of drugs. Access to these capabilities enables it to exploit its discovered compounds. If a product from one of Celltech's portfolio of prestige alliances passes regulatory approval then Therapeutics will receive between a 25% and 45% share of that product's net profits by way of a royalty, without incurring any manufacturing or marketing expenses itself. Third, executives noted that through these collaborations Celltech has over time learned to develop, or deepen, its own initially limited drug development capabilities, such that it now seeks to take on an increasing role in the management of clinical trials, particularly Phase I and II trials. Fourth, alliances with prestige partners bring with them a validation of both Celltech's technology and its corporate strategy. This validation was vital to Celltech in raising its perceived value among investors prior to its launch on the London Stock Exchange in 1993. Post-1997 it was also vital in the recovery of Celltech's share price after the collapse of a Phase III clinical trial and the loss of Bayer as a prestige alliance partner (Mc Namara, 1998). It will be empirically observed in Chapter Four that announcement of prestige alliances have a strong and abnormally positive effect on a biotechnology firm's share price.

From Figure Four it can be observed that prior to 1990 the firm did not have Prestige Alliances partners in Therapeutics. The number of these alliances grew between 1991 from one, to a peak of five alliances in 1995, declining to four in 1997 and 1998. From Figure One it can be seen that the returns from Exploitation in the Biologics firm were declining from 1990 to 1992, with some recovery in margins in 1993 to 1995. During this period exploitation, as represented by Prestige Alliances, was increasing as per Figure Four. Thus declining exploitation in Biologics was partially offset with a rise in exploitation in Therapeutics.

Figure Four offers a set of metrics from which the balance between Exploration and Exploitation that has been achieved within the Therapeutics division can be observed. From Figure Four it can be seen that the amount of Exploration within Therapeutics has risen over time. In 1990 there were two discovery projects and one Phase I clinical trial. By 1998 there were six discovery projects but no Phase I clinical trials; the

renewal of Celltech coincided with a rise in the number of Exploration projects inside Therapeutics. From Figure Four it can be seen that prior to 1993 the number of Exploration projects within Therapeutics exceeded the Exploitation activities, however from 1993 onwards the number of Exploitation activities increase. By 1998 there is a greater emphasis on Exploitation projects than Exploration, suggesting that Celltech may once again be moving out of balance.

FROM CORE RIGIDITIES TO EXPLORATION FOR NEW CORE CAPABILITIES: ACTIONS TAKEN TO PROMOTE EXPLORATION AND EXPLOITATION INSIDE CELLTECH

In 1990 Celltech exhibited many of the characteristics outlined in Chapter Two (Figure Two) that promoted the suppression of Exploration. How did the firm and its management reverse the decline of Exploration and create the more balanced (in terms of Exploration and Exploitation), higher value Therapeutics division? The data contained in the Celltech case revealed the following to be important:

- the existence of a series of crises in 1990, which can be classified as environmental shocks from Chapter Two, Figure Two (as partially reflected in Figure Two of this chapter);
- a new CEO and top management (personnel turnover as per Figure Two of Chapter Two);
- redundancies in the Biologics division simultaneous with the hiring of thirty medicinal chemists, injecting a new knowledge base into Therapeutics (personnel turnover as per Figure Two of Chapter Two);
- the reforming of teams from a functional organisation of technically orientated teams to multi-functional project-orientated teams (changes in interaction structures, as per Figure Three, Chapter Three);
- the development of a shared culture and language across the firm (as per Figure Three, Chapter Two);
- dynamic management of slack and support of a culture of experimentation (as per Figure Three, Chapter Two); and
- the management of alliances to promote both access to resources and appropriation (as per Figure Four, Chapter Two)

The next few pages of this chapter elaborate on what these changes entailed and why they were important.

It was clear that at the end of the 1980s there was a high level of *inertia* and resistance to change from within Celltech. Biologics had been the source of Celltech's revenue growth. The old management had committed itself to a technology focus, not interdisciplinary research. Strong collaborative ties had been formed with academia and were viewed as central to the future of the firm (Dodgson, 1993). At its foundation, the central focus of Celltech had been a technology transfer agreement with the Medical Research Council that sought to exploit academic knowledge commercially. From contemporary annual reports and Dodgson's (1993) study of Celltech's first decade, it can be seen that management was strongly committed to the continuation and strengthening of this agreement, having negotiated in 1988 an extension of the contract until 1993. Employees had come to jokingly refer to Celltech as the 'University of Slough'. One executive noted that:

"Almost a third of its R & D spend was on these [academic] collaborations. I can say that almost universally they were very non-productive. They were quite a cash drain on the company."

On the Therapeutics side, research seemed to lack focus and was largely unproductive (some departments consisted of only two people). Change would have to overcome the firm's past commitment to collaboration with academia, and the accompanying culture, and a reliance on profits from Biologics based upon the development and application of technological capabilities reinforced by academic ties and hierarchical structures.

Creating a crisis

As observed in Chapter Two, Huff, Huff and Thomas (1992) note that shocks are needed to engineer change and that that rarely is a single shock to a managerial system

sufficient. A single shock can be rationalised away as an aberration, or a temporary occurrence. Ordinarily, as in the case of Celltech, a radical departure from the status quo is only triggered by a series of significant shocks to the system, which are bunched closely together. Celltech encountered a series of three distinct shocks. First came the financial shocks of 1989 to 1992. It can be seen from Figure Two that Biologics's gross margins were in considerable decline from 1988 to 1990. The rate of growth of Biologics's turnover was declining over this period, and from 1990 to 1992 was negative. Declining performance over a period of several years could not easily be explained away. Second, Celltech's major shareholder, with a 36.4 per cent stake, went bankrupt in 1990. This placed further pressure on Celltech to address its poor financial performance. Third, the retirement of both the founding CEO and Research Director was scheduled for 1990. This, combined with the two other shocks, offered a window of opportunity in which change could be initiated and inertial forces overcome.

The challenge that these shocks posed should not be underestimated. Shareholder pressure for change was intense. One senior executive recalled the mood of the time, saying:

"It was relayed to us by the original investors that 'You are smart guys. You can tell us a nice story, but how do we know it's valid?' You see, six or seven years ago, very few financial institutions knew anything much about science, let alone the pharmaceutical industry. They felt that they had already been hoodwinked by one group of management and so what they said was we had to do something quite distinctive that made them believe there was something special about us."

To impress the shareholders new directions in strategy were necessary, new capabilities had to be developed and scarce resources refocused, thus the firm invested in the process of Exploration. A new management team was hired which had to drive Celltech towards its ultimate goal of becoming a large R & D-led company that took drugs to market. The old capability focused on the contract manufacturing of antibodies and collaborative links with universities to maintain a leading edge functional technology focus (Dodgson, 1991; 1993). New capabilities needed to be

developed to focus on new product development, rather than technical excellence. As one executive commented,

“An organisation of this type is not judged by the output of scientific papers. It is actually judged by its ability to come up with technologies which in turn will lead to therapeutic entities. The technology itself is fairly valueless until you convert it into something practical... What I think we emphasised, if anything, was to say that, if that is the basis on which we are judged, then clearly if we cannot convert our technology into practical realities, we will be complete failures.”

Unlearning, reorganising and new recruits

As noted in Chapter Two unlearning plays a crucial role in the stimulation of Exploration (see Figure Two, Chapter Two). In the case of Celltech the switch from technological capability to a more therapeutic-based capability was a considerable challenge. Renewal was not just a matter of changing strategic direction. More fundamentally, it required a change in the way staff thought about science and how research was organised. This ideological change is encapsulated in the move away from an almost academic culture, where close collaborative ties with academia were mirrored in structures that executives described as like an academic institution. As one executive commented, change required a shift away from an academic philosophy of technical excellence, measured in part by the number of scientific papers published, and towards a more commercially-minded focus on getting products into the clinic. Another executive noted that this required “almost a sea change in the way that we were organised.”

Research was reorganised with teams focusing around three therapeutic targets selected by the new management. Biologists of differing specialities were put in teams to work towards a common goal. Previously they had worked within functional groupings. Now scientists of differing functional expertise worked together within specific projects. Each project had a goal of bringing a drug to clinical trials, thus

improving the firm's research productivity. This meant that teams no longer focused on the development of technical expertise alone, but upon the combination of technical expertise to develop novel therapeutic compounds.

Mixing old and new functions within common projects required scientists to learn about issues outside their previous speciality. To do this they had to focus more on these skills and less on their specialist skills, which had been their sole previous focus, thus facilitating unlearning. This process of socialisation, a new challenge, a new vision of the future, and a narrowly defined focus of work (three therapeutic areas with individual teams looking at narrower issues) enabled a shift in capability to occur. (The success of this strategy, in terms of research productivity and acceptance by stakeholders, cumulated in the divestment of Biologics.)

As noted in Chapter Two, Intellectual Diversity is essential for change from Core Rigidities towards Exploration to create new capabilities (Carley, 1992; Simon, 1991; Javanovic and Nyarko, 1995). It was the new senior management recruited from outside Celltech which brought with it this new perspective on how the firm could achieve success. Additionally, the senior management team brought new skills, including knowledge of asthma therapies, which had not previously been a focus at Celltech. The strategy also involved hiring 35 medicinal chemists who were dispersed across the projects as required. These new staff members enlarged Celltech's skill base from biotechnology and into the more traditional medicinal chemistry skills of pharmaceutical firms. From this discussion it can be said that Celltech initially experienced organisational inertia and switching costs, which as Chapter Two notes encourages the maintenance of Core Rigidities. Through a series of environmental shocks, personnel turnover and unlearning Celltech was able to harness Intellectual Diversity within the firm necessary to promote the process of Exploration for new organisational knowledge and capabilities in the R&D of innovative drug compounds.

Systems to foster the coexistence of Exploration and Exploitation

What other factors did Celltech use to engineer the change? As noted in Chapter Two changes in Social Interaction play a vital role in stimulating Development, while changes in the levels of Intellectual Diversity stimulates Exploration. Celltech's new management stimulated both of these characteristics promoting both Exploration and Development. This involved both the stimulation of Social Interaction through informal mechanisms and creation of formal review systems to ensure both effective Exploration for new knowledge and Development of current stocks of knowledge, in addition to maintenance of a balance between Exploration and Exploitation activities.

The new management of Celltech paid particular attention to managing Exploration for new knowledge and Exploitation of the knowledge derived from Exploration activities by creating a series of systems to manage drug discovery and development. The management of current projects and the search for new research ideas involves both formal and informal systems. Close proximity is an informal mechanism; all staff are located on one site and the layout of the building is specially designed to facilitate interactions. More formal mechanisms include quarterly reviews of the progress of projects. If they are not meeting objective milestones, then reasons are elicited from the team. If senior management believes that these problems are not solvable within the present budget and time frames due to resource or capability deficiencies, then projects are quickly shut down. Annual reviews enable the scientists to interact with senior management in budget allocations for the coming year. Strategic research reviews are conducted periodically. Through these reviews, ideas on new projects bubble up. Often the original ideas upon which new project proposals submitted during the research review are based stem from the conferences which the scientific staff have attended, or literature they have read, in which interesting ideas were raised and then independently pursued by themselves during slack time. A senior executive describes the essence of how new ideas bubble up, culminating in the strategic review, as follows:

“You don't say that we are going to have a meeting next Thursday. There usually is a lot of discussion about the ideas. Eventually they [the proposals]

come forward, but they don't come forward as a surprise on Thursday afternoon, to be decided by the end of the day. Because we are a small company you are always talking to people, so you have a good idea of what ideas are being discussed. It is almost a constant process of seeing what's new, what we might do, what's exciting."

Common codes and shared language

As noted in Chapter Two creation of a common language plays an important role in the Development of stocks of organisational knowledge. Creation of a common language and interaction across functional disciplines (Chapter Two, Figure Three) played an important role in the renewal of Celltech. When the firm changed from a discipline and technology-based capability to a therapeutic capability, chemists were thrust together with biologists leading to differences in common understandings. Disciplines that within Celltech had previously worked in hierarchical isolation now had to converse and work side by side on an operational level to integrate their diverse knowledge into the production of a single drug. This required colleagues to train each other in the basics of their discipline. In so doing, knowledge overlaps and redundancies were created. An understanding of the language and mindsets of other disciplines facilitated a deeper understanding of the problems facing the firm. Triggers for innovative solutions were set off through this process of developing shared understanding at the level of bench scientists. The Director of Research summed up the effect of putting people with different skill bases into common teams by noting:

"We were very much organised along technical disciplines for quite a long time, which gave us a very good strength in technology but maybe not a good strength in biology. We found that when we moved into the therapeutic areas we were able to get people to be focused on biological questions so that they built up their biology base. So we had people who had a lot of interest in inflammation, and these people built up a knowledge base around inflammation as opposed to being molecular biologists, or cell biologists or biochemists." The reorganisation "challenged [researchers] with learning

more about the biology, rather than just learning about techniques and technology.”

Exploration and Exploitation of a Collaborative Capability

As argued earlier in this chapter participation in an alliance network is a vital value adding task for biotechnology firms as it facilitates both development of drugs and appropriation of a return. One can see from Figure Four that between 1991 to 1998 Celltech has increased its number of prestige alliances. Such alliances facilitate both Development and Use for Appropriation. Celltech’s alliance network enables it to access world class development projects, thus they argued, increasing the speed and reducing the cost of gaining regulatory approval for promising trials. Collaborative agreements also enabled Celltech to appropriate a return from the stocks of knowledge they had in development. As noted earlier this has raised £26.5 million in cash payments, with the potential for more milestone payments and downstream royalties.

To create its network of four prestige alliance partners and numerous other partnerships with smaller pharmaceutical firms and research institutes Celltech had to create a collaborative capability. This is described by the senior management as an ability to interact with major pharmaceutical firms. The management argued that the difficulty lay not so much in the identification of collaborative partners, nor in the structuring of collaborative agreements, but rather in the management thereof. Identification of partners was sometimes quite obvious, as in the case of the Celltech-Bayer alliance where Bayer were the only major pharmaceutical firm to have a similar patent portfolio to Celltech in the area of anti-TNF. The real problem rose in the development of an understanding of how large pharmaceutical firms manage projects and their relationships with biotechnology partners. Here the development of a shared language was vital. The need to share language at the operational levels of the firm was mirrored by the need to create a shared understanding with external collaborators. The search for and management of external collaborations was conducted at the middle and higher levels of management. Senior management at Celltech found that its collaborators tended to think differently. This makes communications across firm boundaries a slow process, where firms learn to talk to each other, and learn the

meaning of their objectives, mindsets and systems, thus slowing the transfer of knowledge needed to collaborate.

An example was Celltech's collaboration with Bayer. The decision-making structures of the firms were quite different. Bayer focused on in-depth commercial analysis of the project first and then on meticulous large-scale clinical trials. According to a Celltech executive, decisions taken by the Bayer members of the project team sometimes needed to be ratified by several layers of management. Celltech did not focus on commercial analysis in as much depth as Bayer, nor did it have a lot of experience as a company in conducting large-scale clinical trials, especially at Phase III. Celltech's expertise was in the discovery of novel compounds, and there was only one level of management between the project manager and the CEO. These issues, amongst others, led to different ways of working in Celltech and Bayer. To work together these alternative systems had to be understood by the Celltech management and accommodated for. This initially slowed the project, however it offered excellent opportunities to learn the management of alliances with large firms. This process can also help a firm to recognise and learn of gaps in its own knowledge bases, stimulating the managerial processes of both Exploration and Exploitation. For example, Celltech recently hired a senior manager with expertise in the marketing of pharmaceutical products to fill a gap in its knowledge of commercial analysis. Its expertise in clinical trial development has been deepened through learning from alliances with Bayer and other large pharmaceutical firms, all of which are widely experienced in the management of large-scale clinical trials.

DISCUSSION

The renewal of Celltech provides five key lessons. First, contrary to suggestions in the literature, renewal is possible through a movement away from Exploitation and towards Exploration. The key to such a renewal strategy is that it be based firmly on the principal of adding shareholder value. By moving away from the low margin but profitable Biologics, and towards loss-making drug discovery and development, the firm increased its market value. During this period the firm raised a further £41.7 million from shareholders. The new management realised that shareholders were not

interested in short-term profits but rather in longer-term capital gains. Paradoxically, bigger losses that focus on the right sort investments can mean bigger potential gains. By intensifying investments in Exploration to develop a strong Therapeutics division, the capital value of Celltech rose, despite an intensification of losses to £75.9 million due to increased R & D.

Celltech moved to Exploration not just in terms of new scientific capabilities, but also in terms of new managerial capabilities. This is a key lesson of the Celltech renewal. Renewal based on Exploration requires co-ordinating changes in both technical and managerial capabilities. Celltech would have failed if it had only renewed its technical capabilities and ignored the creation of capabilities in managing collaboration and a new relationship with shareholders.

The second lesson is that the management of crisis and galvanising the commitment of key organisational actors is essential in overcoming organisational inertia to renew and trigger fresh Exploration. This is not a new lesson, having been championed by Pascale (1990), Baden-Fuller and Stopford (1994) and others. In Celltech, new management entered the firm but was cautious at first, galvanising the commitment of a key group of scientists and administrators prior to announcing the change in strategy from technology focus to project groups orientated around the creation of individual drugs. Having gained the commitment of the key scientists in the firm the sense of crisis, which had been growing amongst staff, was relieved. The new team also brought with it a sense of credibility, being made up of accomplished research scientists and pharmaceutical administrators from Roche Holdings, amongst others. The key here is that a relatively small number of new managers stepped into the crisis, untainted by its past, galvanised a small number of key actors within the organisation, and then presented the staff with a new strategic vision which was not only endorsed as acceptable by shareholders, but which also excited and motivated staff. As one manager put it, the staff were released from the constraints of contract manufacturing and research, in which they had no long-term stake, and could now engage in big, liberated science where their scientific skills and creativity could be profitability pursued.

The third lesson is that for a firm to renew based on Exploration it needs to stimulate knowledge creation through an injection of both external and internal diversity. External diversity was infused through the arrival of the new senior management team. This brought new ideas on what the strategic focus of the firm should be, in addition to a knowledge of how large pharmaceutical firms operate, which was fostered to develop a capability in managing prestige alliances. External diversity also came in the form of the new medicinal chemists. Inappropriate knowledge was partially extinguished by the redundancy of 60 staff, which when combined with structural changes signalled that the old ways of doing things were not to continue. Internal diversity was stimulated by the creation of the new teams organised around drug projects. Executives noted that the majority of new project ideas came from the creative resources of those staff who existed in Celltech prior to 1990. In terms of stimulation of Exploration, as outlined in Chapter Two (Figure Two), personnel turnover, unlearning and environmental shocks all played an important role.

The fourth lesson from the Celltech case is that improvements in the process of Exploration need not come at the cost of the process of Exploitation. At the same time as creating an environment in which Exploration was encouraged and managed, Celltech's management also took action to deepen its development process. The process of Development was also promoted through by creation of a common language and interaction both across functional boundaries within Celltech and across organisational boundaries via alliances. Dynamic slack was also managed to stimulate Development. By moving staff away from contract manufacturing and research and into three drug discovery projects Celltech was able to greatly speed development of its most valuable stock of knowledge, namely, compounds which Celltech owned itself as opposed to developed on contract for other firms. In terms of promotion of Development, as outlined in Chapter Two (Figure Three), dynamic slack, interactions across organisational structure and common language all played an important role.

The fifth, and most important, lesson from the renewal of Celltech is that for Exploration to be sustained it is vital that systems be installed to ensure that the

outputs of Exploration activities are clearly linked to the firm's exploitative efforts. Systems played two vital roles. First they sought to efficiently manage the processes of Exploration and Development individually. Failing projects, be they Exploration or Development, were identified quickly and either corrected or eliminated. Secondly, systems were put in place to manage the linkage between Exploration and Exploitation activities.

These systems occurred at two levels of the organisation. At the operational level, new capabilities in interdisciplinary research were developed. At the upper management level, capabilities in the management of collaboration were developed. Regular research reviews were initiated which enabled an Exploration (discovery) project to be assessed in terms of its ability to deliver tangible results in a timely and cost effective manner, and the ability of the project to attract and retain collaborators (the relationships with which were identified, cultivated and managed by senior management). As drugs exited discovery projects, they were assessed by a Product Development Panel, which sought to assess if each drug should move into the Development, or Exploitation, stage of the R & D process. These systems ensure that a tight linkage between Exploration and Exploitation is maintained.

Systems were also put in place to ensure that a balance between Exploration and Exploitation was maintained over time. As drugs exit the discovery stage, the research review process seeks to identify new discovery projects. Ideas bubble up from the operational level and are assessed by the middle management, and reviewed by senior management. This process, coupled with a system of strategic review, seeks to ensure that Exploitation does not drive out Exploration in Celltech. This temptation is real because as a drug moves through Phase II and III trials the costs rise dramatically, while the time to market is diminishing. The temptation is to cut investment in discovery projects so that these funds can be devoted to late stage clinical trials.

The Celltech case also offers insights into propositions one, three and four of Chapter Two. The analysis of Celltech demonstrates that a real firm can be analysed using the conceptual lens of Exploration and Exploitation. Measurements can be created to

observe Exploration, Development and Use for Appropriation in real firms. This lends support to the contention in proposition one in Chapter Two that Exploitation can be characterised as Development and Use for Appropriation and that these concepts should be able to be measured in a real organisational context.

The analysis of Celltech also offers some insights into proposition three, namely, that greater value can be obtained when Exploration, Development and Use for Appropriation are managed as an integrated whole, rather than as separate portfolios. Prior to 1990 Development and Use for Appropriation took place in the separately managed contract manufacturing division. It was marginally profitable. Within the research division exploration for new compounds was undertaken, but this was not linked to Use for Appropriation or Development. No drugs were in the Phase II/III development stage and no innovative methods were being employed to appropriate a return from Exploration activities. The firm was near bankruptcy and its shares were illiquid. The new management took an overarching view of Exploration, Development and Use for Appropriation. In the Therapeutics division Exploration was linked to Development via managerial review systems. Management were innovative in how they communicated the value of Exploration activities to shareholders by initiating Prestige Alliances that validated the value of the knowledge being created inside Therapeutics, in addition to providing a return in the form of milestone payments and transfer of costs. The result was that, despite intensification of net losses, Celltech shares are now more liquid and the firm is the eight largest independent biotechnology firm in terms of market capitalisation (Mc Namara, 1999).

The case also offers some insights into proposition four. The Celltech case illustrates that balance between Exploration and Exploitation can be maintained beyond the short term. This period of balance coincided with a rise in the value of Celltech on the stock market. The experience of Celltech also casts some light into how balance may be maintained, namely through the installation of managerial systems that seek to link Exploration and Exploitation efforts, coupled with innovations that facilitate the early Appropriation of a return from Exploration activities.

CONCLUSIONS

Theoretical development has posed a challenge to organisations. On the one hand they are told that they must balance Exploration activities with Exploitation activities if they are to maximise their value. On the other hand, firms are told that in general, maturity brings inertia and decline as Exploitation drives out the creation of new ideas. All too often, people have drawn the conclusion that high technology firms live on a knife edge and that having fallen, renewal is likely to be almost impossible (Christensen, 1997) or the result of serendipity (Burgelman, 1994).

The Celltech case study throws into doubt some of these theoretical presumptions. The Celltech case documents the renewal of a high technology firm from near bankruptcy and paralysis to a high level of success. More importantly, the case demonstrates that this renewal was not 'accidental', but rather the application of well tried and tested managerial techniques which included a new CEO, the hiring of new staff from a different discipline, the formation of new team structures and the infusion of new organisational processes.

Much of the past research into the balance between Exploration and Exploitation has relied on the generation of mathematical models as opposed to organisational case studies (Levinthal, 1997; Cohen and Levinthal, 1994; 1990; March, 1991). Instrumental cases can be useful in theory testing (Eisenhardt, 1989) and theory extension (Yin, 1989) or theory development (Sutton and Straw, 1995). The Celltech case was carefully selected such that it could act as an instrumental case to enable Exploration of whether or not it was possible both to renew based on turning back the tide of Exploitation and to maintain a balance between investments in Exploration and Exploitation. The literature would suggest that both phenomena are difficult, and by implication rarely achieved. By employing an alternative method to prior research, based on a longitudinal case study as opposed to a mathematical model, this chapter has offered further insights into both the process of renewal and the management of the tension between Exploration and Exploitation inside a high technology firm.

FIGURE ONE: INPUT MEASURES OF EXPLORATION/EXPLOITATION BALANCE: ALLOCATION OF RESOURCES

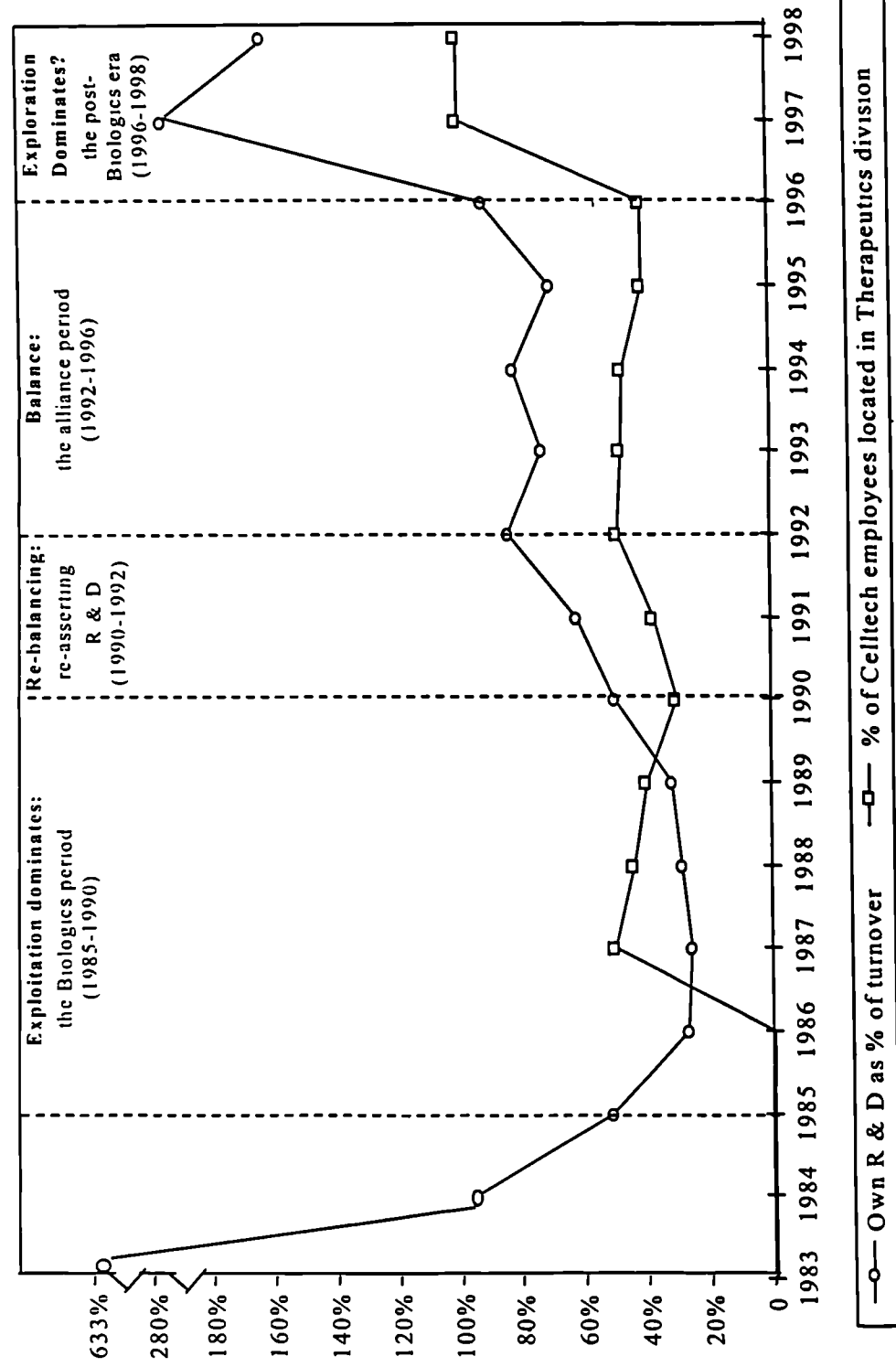


FIGURE TWO: PERFORMANCE OF CELLTech BIOLOGICS

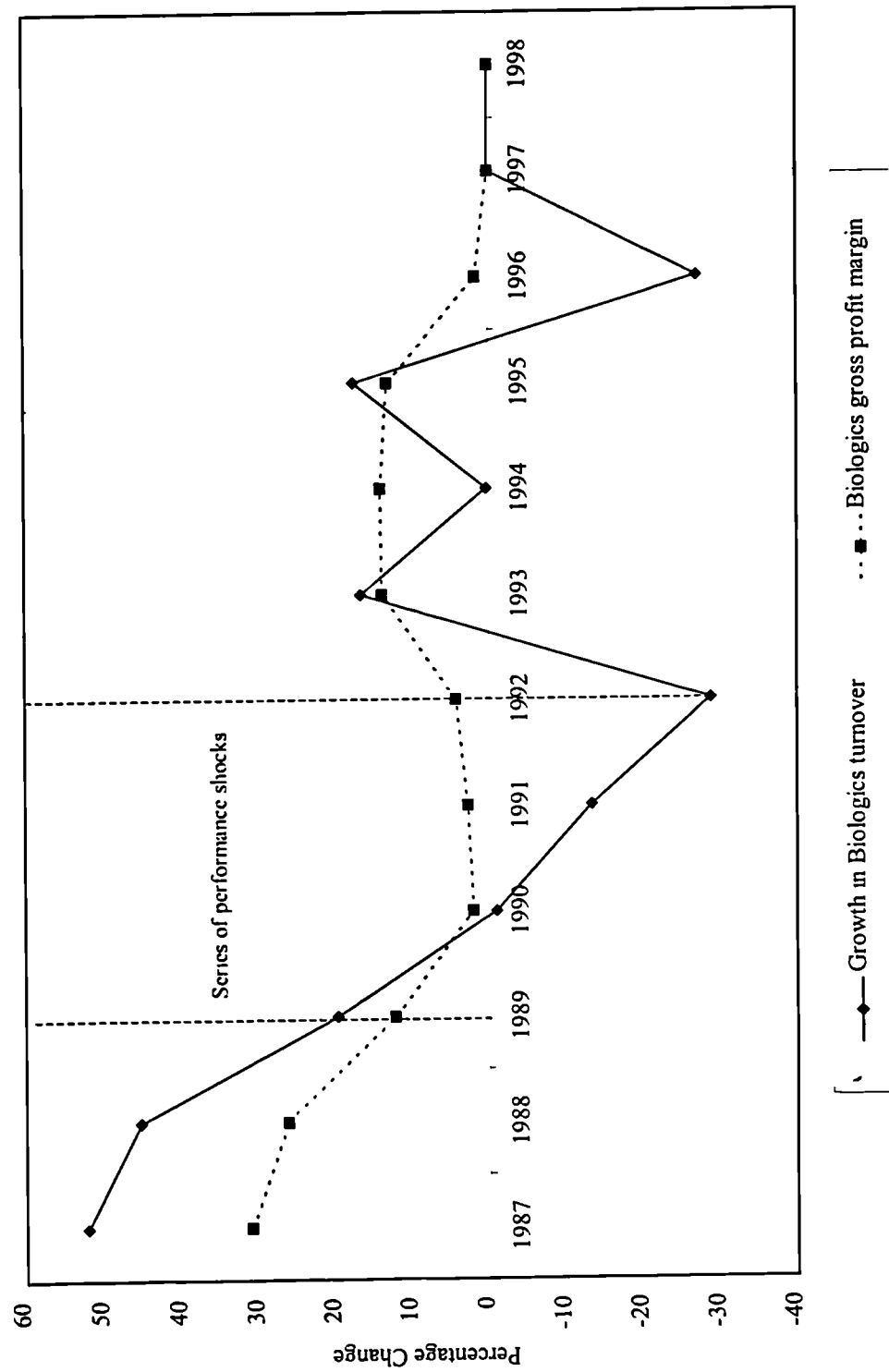


FIGURE THREE: OUTPUT MEASURES OF EXPLORATION/EXPLOITATION BALANCE: REVENUE

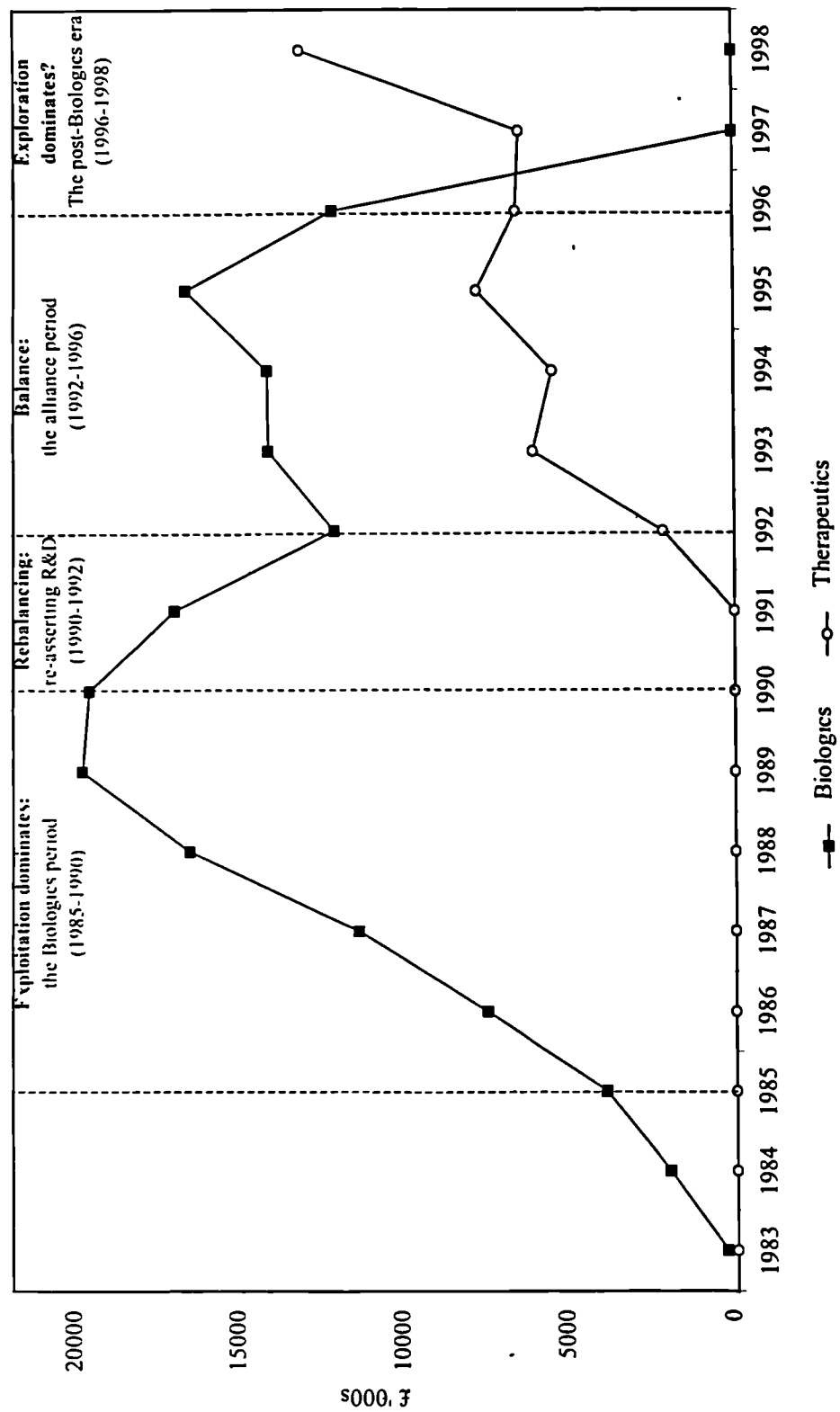
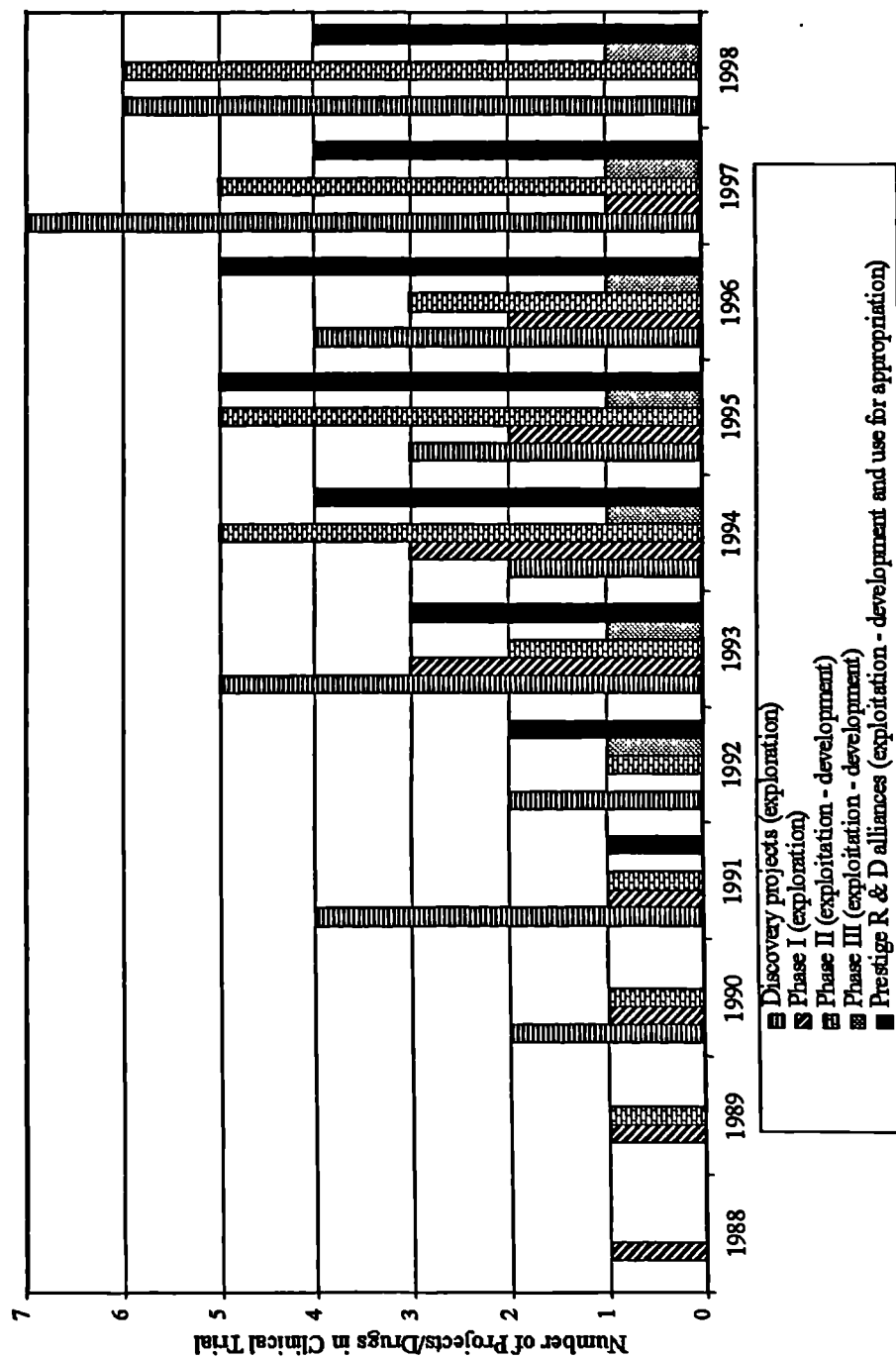


FIGURE FOUR: BALANCING EXPLORATION AND EXPLOITATION IN THERAPEUTICS



Chapter Four:

Wealth Effects of Announcements on Exploration and Exploitation Events amongst UK Therapeutic Biotechnology Firms

INTRODUCTION

In Chapter Two the theoretic relationships between Exploration and Exploitation were outlined. In particular it was noted that prior literature has argued that balance is difficult to maintain and that there is an in build bias towards Exploitation, due to shorter feedback loops and more positive financial returns (March 1991; Levinthal and March 1993). In Chapter Three it was shown, through the lens of the longitudinal Celltech study, that in a real organisational context it was possible to balance Exploration and Exploitation for over half a decade and that renewal was possible by moving away from the dominance of Exploitation and towards Exploration. The Celltech case clearly indicated that investments in Exploitation had been the key to the firm's success in the 1980s. Re-focusing around Exploration had been the key to the firm's turnaround in 1990, while maintaining a balance between Exploration and Exploitation through the 1990s was essential in maintaining the momentum of the 1990 turnaround.

As Chapter Two illustrated, the management of the Exploration/Exploitation dilemma is an important academic topic. The Celltech case illustrates that within a particular organisational and temporal context the management of this balance is an important aspect of value destruction and creation. The next logical question to ask is whether or not the management of Exploration and Exploitation in general adds shareholder value? If it does then this is clearly both an important academic and managerial issue. This chapter seeks to answer the question of the wealth effects of knowledge Exploration and Exploitation activities through the lens of an event study.

Chapter Three classified key events, for biotechnology firms as being either Exploration or Exploitation activities. The choice of events was driven by what managers in all three case companies identified as being of critical importance in the successful management of a UK biotechnology firm. The case studies are provided in full in the appendices. Drug Discovery and Phase I clinical trials were defined as Exploration events, Phase II/II clinical trials were defined as Exploitation activities, while alliances were defined as predominantly Exploitation but with Exploration elements. This chapter undertakes an analysis of all announcements of progress in these events made by UK publicly quoted biotechnology firms over a three-year period. The goal is to assess whether shareholder reactions to such announcements suggest that such activities add shareholder value, and if so which activities have the greatest effect on wealth. A wealth effect occurs if, in reaction to the announcement, the share price of the firm either rises or falls at a significantly greater level than one would expect the share price to perform in the absence of the announced event.

The underlying argument in this thesis to date suggests that positive announcements about the firm's Exploration and Exploitation activities should have a positive effect on wealth. Chapter Two suggests that from a *theoretical standpoint* the wealth effects of Exploitation activities are greater than Exploration. Chapter Three clearly indicates that within a *single organizational context*, namely Celltech, both activities add value, but the extent of the value created is dependent on the organizational context. This chapter will quantify the extent to which Exploration and Exploitation activities add value using a sample of all UK public biotechnology firm's between December 1995 and January 1999, thus providing a *quantitative insight as to whether in general* Exploration or Exploitation activities add greatest value..

This study is the first, to the knowledge of this researcher, that uses the event study methodology to assess the theoretical bias identified by Levinthal and March (1993) that Exploitation tends to have a stronger positive financial feedback from the market than Exploration activities. The classification of key organizational events into Exploration and Exploitation makes such an empirical Exploration of this issue

possible. This research is also the first to jointly explore the wealth effects of alliance making and progress in the stages of the R&D process. It is true to say that the impact of inter-organizational cooperative agreements upon shareholder wealth has been explored in the literature. Such studies have examined the shareholder wealth effects of equity joint ventures within single sectors such as Information Technology (Koh and Venkatraman, 1991) and multiple sectors (Madhavan and Prescott, 1995; Mc Connel and Nantell, 1985; Reuter and Miller, 1997). Event studies have also assessed the effect of non-equity based strategic alliances within multiple sectors (Chan, Kensinger, Keown and Martin, 1997; Das, Sen and Sengupta, 1998) and single sectors such as biotechnology (Stuart, Hoang and Hybels, 1999). The sample of these studies has, however, been exclusively or predominantly US, thus insights into the shareholder wealth effects of alliance making for UK firms are sparse. An event study have also been employed to examine the shareholder wealth effects of announcements of progress in the R&D process across multiple industries (Kelm, Narayanan and Pinches, 1995), though this study is both confined to the US and excludes biotechnology firms.

This chapter seeks to make four contributions to the literature. First, and most important, it seeks to apply the theoretical lens of Exploration/Exploitation to shareholder wealth creation via the event study methodology. This will potentially offer important insights into the relative financial return of Exploration and Exploitation activities in the eyes of shareholders and support, or cast doubt upon, Levinthal and March's (1993) assertion that Exploitation comes to dominate over Exploration due to faster and casually unambiguous financial feedback loops. Second, it is the first study, to the knowledge of this researcher, to offer insights into both the shareholder wealth creation effects of alliance making and progress in the R&D process within a single sample. This chapter will offer researchers potentially important insights into shareholder's assessment of the relative importance of each of these activities upon wealth creation. Third, the study will partially fill an important gap in the literature whereby the wealth impacts of alliance making and progress in R&D are well known for US listed firms, but not for UK firms. Fourth, the study will offer insights into the process of wealth creation side of UK biotechnology, which the

UK government has identified as a strategic growth sector (Office of Science and Technology, 1999).

The remainder of this chapter will be split into five sections. The first section will provide a brief whistle-stop tour of the event study literature in both Strategic Management and Financial Economics. A brief explanation of the event study method is offered at this stage. It will also highlight some of the major research themes that the event study methodology has been employed to explore. The results of various studies within and across the literatures are briefly contrasted. It is observed that event studies employed to explore the same theme can generate both confirmatory and conflictual data. Event studies which focus upon the wealth effects of alliance making and progress in the R&D process are not discussed in this section, but will be employed in the hypothesis and discussion sections. It shall be noted that though studies in Financial Economics have challenged this method, its core assumption, that of the efficient market remains robust enough that the event study methodology to justify its continued application in modern academic studies.

The second section will develop six hypotheses that enable the researcher to test the value adding nature of announcements of alliances and progress in discovery, Phase I, II and III clinical trials. This enables one to more generally test whether Exploration or Exploitation adds greater value in the eyes of the shareholder. These hypotheses shall be developed through references to prior research in the literature and observations based on the Celltech, Oxford Molecular and PolyMASC case studies (see Appendices). In the third section I will outline the methodology employed in this chapter, detailing sample selection and the implementation of the event study methodology.

The fourth section will analyze the effect of all announcements made by biotechnology firms listed on the LSE over a three-year period to test the five hypotheses. It shall be observed that in general the announcement of all four events had a significant and very large positive effect on shareholder wealth. A hierarchy of value effects will be observed, whereby, Prestige Alliances add the greatest value (over 10% abnormal

returns on the day of the announcement), followed by progress in Phase II/III clinical trials (over 9% abnormal returns), Regional Alliances (over 5% abnormal returns) and finally, progress in Discovery/Phase I (over 2% abnormal returns). Alliance events were found to have a marginally higher abnormal return the day of announcement (7.74%) than announcements of progress in R&D (7.11%), however the standard deviation of alliance events was lower than R&D events (7.84 and 11.27 respectively). In the fifth section implications that these findings have upon the theory of knowledge Exploration and Exploitation will be discussed.

A WHISTLE-STOP TOUR OF THE PREVALENCE OF EVENT EFFECTS

Brief explanation of what an event study does.

The methodological details of event studies are discussed in the methods section of this chapter, however a brief explanation of what event studies are all about may be of help to the reader. Underpinning the event study methodology is the efficient market hypothesis, which argues that all publicly available information that offers insight into the present and future performance of a share is promptly digested by the market and reflected in a firm's share price (Fama, 1991). Thus the share price of a firm should reflect shareholders' assessment of its future earnings potential. Returns in excess of market performance should not persist beyond the short-term period (a matter of minutes or in extreme days) required to assimilate the new information into a firm's share price. In periods where the market received no specific information on the future performance of the firm its share price should broadly follow the performance of the market around a random walk where prices are as likely to rise as fall. It is vital to the maintenance of the efficient market hypothesis that evidence not emerge which reveals that shareholders consistently over, or under, react to announcements that have an impact upon firm valuation. Such evidence would break the assumption that share price fully reflects the earnings potential of the firm. Equally it is important that evidence does not emerge that persistent long-term abnormal returns associated with a single event do occur. Such evidence would break the assumption that new information is rapidly and completely assimilated into the price of a share.

The essence of an event study is to assess shareholder reactions to unanticipated announcements that provide new information about a firm and see if they have an impact on share price. Such announcements should offer the shareholder new, or additional insight, into the current or future performance of the firm. The events need to be unanticipated because otherwise the information that they provide about the firm should have been already assimilated into the firm's share price. If the event conveys positive news then one expects share price to rise, while a price fall would be expected in response to negative news. For an event effect to be deemed to have occurred then such share price movements need to be significantly different from the 'normal' behaviour of the firm's share price. Such significant differences are referred to as 'abnormal returns.' Determination of the normal behaviour of a share is at the heart of the event study method and is discussed in the methodology section.

Some event studies in the management and financial economics literature.

The event study methodology has a long and rich history in the empirical literature since its introduction into modern academic studies by Fama, Fisher, Jensen and Roll in 1969. A wide variety of research topics have been explored through the lens of event studies. Within the Strategy literature, shareholder wealth has been found to be significantly effected by events as varied as top management changes, downsizing and restructuring, strike commencement and settlement, product recalls, Mergers and Acquisitions and socially responsible and irresponsible corporate behaviour. Within the Financial Economics literature research event studies on the same topics as of Strategy have included studies on the impact of top management exit from firms, the effects of downsizing on firms and their competitors, product recalls and Mergers and Acquisitions. Financial Economists have focused on a wide range of other issues, primarily the search for systematic anomalies in the randomness of share price movements, which could cast doubt on the validity of the event study methodology, and also the effects of key changes in financial structure upon share price. Some of the more exciting structural observations from these studies have included: the existence of persistent abnormal returns for small firms in January, known as the 'January effect', that Initial Public Offerings appear to be consistently under priced and that stock splits

appear to result in persistent abnormal returns. A brief overview of some of the studies from the Strategy and Financial Economics literature demonstrates not only the widespread usage of event studies but also both the occurrences of reinforcing and contradictory results that different event studies examining the same issue can generate.

Worrell, Davidson and Glascock (1993), observed positive abnormal returns upon the dismissal of a CEO if a successor is announced at the same time, while negative effects were observed in the run up to a dismissal. Worrell, Davidson, Chandy and Garrison (1986) observed that the death of a Chairman was accompanied by positive abnormal returns, while the death of a CEO met with a negative market reaction. These results have been used to support the hypothesis that who is in control of senior management matters to shareholders. Observations from the Financial Economics literature complement the argument of strategy that senior management matters to shareholders, by observing that the departure of a senior manager, Chairman or CEO, to a rival firm results in negative abnormal returns, while sudden death results in positive abnormal returns.

Interestingly it has also been shown through event studies in the Strategy literature that shareholders value the layoff of workers in general, though for different reasons. The layoff of workers is argued to be a signal to shareholders that a firm is responding positively to a market challenge, or cost inefficiencies, resulting in positive abnormal returns in both US and Japanese firms (Lee, 1997). In US firms it has been found that shareholders react positively to layoffs associated with a restructuring strategy, while they respond negatively to layoffs linked to financial distress (Worrell, Davidson and Sharma, 1991). Studies in the Financial Economics literature somewhat contradict the findings of the management literature observing not only that layoff announcements trigger negative abnormal returns, but that these spill over to competitors suggesting that layoffs signal to shareholders that the industry in general is in recession (Sun and Tang, 1998). Thus it can be concluded that while layoffs have a strong impact upon shareholder wealth the direction and causality of the relationship remains a matter of debate.

Studies on the effect of product recall upon shareholder wealth appear to be in broad agreement within and across the literature. Significant product recalls result in negative abnormal returns. Davidson, and Worrell (1992) observed that recalls of cars by US manufacturers resulted in negative abnormal returns, with the greatest negative effect occurring when the recall was accompanied by an offer of replacement or cash back rather than repair. This builds on the work of Jarrell and Peltzman (1985) who observed negative abnormal returns across both the car and ethical drugs industry for firms who initiate product recalls. Hoffer, Pruitt and Reilly (1988) further observed that for major US manufacturers product recall by one firm resulted in negative abnormal returns for both it and its competitors, supporting the hypothesis that product recall has industry spillover effects.

A central concern of both the Strategy and Financial Economics literature has been the impact of announcements of Mergers and Acquisitions upon shareholder wealth of both buyers and sellers. Lubatkin (1987) observed from a sample of 1,031 mergers between 1948 to 1979 that pre-merger performance for acquiring firms was positive and significant, while post merger performance was not statistically significant. Singh and Montgomery (1987) observed from a sample of 105 acquisitions larger than \$100 million that acquirers experienced greater positive abnormal returns where the acquisitions were related. Financial Economists have explored the effects that method of payment and ownership of the target firm have upon abnormal returns of acquirers. In agreement with the Strategy literature Travlos (1987) observed from a sample of 167 acquiring firms between 1972 to 1981 that acquirers experienced larger abnormal returns where the offer was in the form of a stock swap as opposed to a cash offer. Chang (1998) examined the effect of announcing an acquisition of a private company. In agreement with the findings of Travlos (1987) it was observed that positive abnormal returns were associated with stock offers, however negative returns were linked to cash offers. From this literature it can be concluded that the initial announcement of an acquisition can be largely, though not always, associated with a positive event effect. This review suggests that the results of Strategy versus Financial Economics studies are largely complementary in the field of product recall and

Mergers and Acquisitions, while mixed in the field of management turnover and layoff announcements.

Management scholars have also explored the effect of strike action and social responsibility upon shareholder wealth. Davisdon, Worrell and Garrison (1988) observed that negative abnormal returns are associated with the announcement of the commencement of a strike, while no effect is observed upon the announcement of settlement or avoidance of a strike. Strikes of less than 20 days in duration, however, can be associated with very small positive abnormal returns. Frooman (1997) conducted a meta-analysis of 27 event studies that explored the relationship between corporate social responsibility and shareholder wealth. Frooman concluded that socially irresponsible behaviour, such as product recalls, criminal misconduct, or antitrust suits, resulted in negative abnormal returns. Menzar, Nigh and Kwok (1994), found in common with other studies that announcement of divestment of South African operations resulted in negative abnormal returns. Wright, Ferris, Hiller and Kroll (1995) observed that for a US sample between 1986 to 1992, negative abnormal returns were associated with socially irresponsible behaviour, where firms were found guilty of major discrimination, while socially responsible behaviour, where firms received Exemplary Voluntary Effort Awards, were associated with positive abnormal returns. It should be noted that replication work by Mc Williams and Siegel (1997) casts doubt on the methodological validity of much of the social irresponsibility event study literature. Notwithstanding their critique one can conclude that in general event studies suggest that social irresponsibility is linked to negative abnormal returns.

The 'January Effect', IPOs and Stock Splits: a challenge to an efficient market hypothesis?

As noted above the Financial Economics literature has also devoted considerable attention to the existence of persistent abnormal returns associated with financial structuring events. It has been empirically shown that between 1927 to 1993 small firms quoted on US exchanges have experienced abnormal returns every January (Beller and Nofsinger, 1998). This phenomena, referred to as the 'January effect', was

brought to the attention of the modern Financial Economics literature by Rozeff and Kinney in 1976. Numerous hypotheses for the persistence of the 'January' effect have been proposed. Beller and Nofsinger's (1998) study supports the investor behaviour hypothesis, where shareholders sell in December to realise tax losses and re-purchases occur in January, while Ritter and Chopra (1989) reject this hypothesis in favour of portfolio re-balancing. Whatever the cause of the 'January' effect its persistence may challenge the notion of an efficient market. Given that the 'January' effect is well known one would expect, under an efficient market, that this information be assimilated and acted upon, thus market actors should anticipate the arbitrage opportunity and act upon it by buying in December and selling at a profit in January.

In a review of prior studies, Smith (1986) reported that studies have found 2 day abnormal returns for IPO stocks to vary from 11.4% during the period 1960 to 1969, based on a sample of 120 firms, to 18.8% over the period 1960 to 1982, based on a sample of 5,162 firms, to a high of 48.4% during the period 1980-1981, based on a sample of 325 firms. Short term IPO under-pricing can be linked to the underwriter's desire to ensure that uninformed customers obtain positive first day returns and invest in future IPOs issued by that underwriter (Beatty and Ritter 1986). There exists evidence that over a long time horizon of three years IPO stocks subsequently underperform a size matched portfolio by 17% (Ritter, 1991). Krigman, Shaw and Womack (1999) observed that IPOs of firms who achieve positive abnormal returns on the first day of trading continue to do so for the first year, while poor performers continue to perform badly for a year. Informed investors, aware of both initial short run under pricing and the persistence of long term winners and losers in the IPO market, flip poorly performing IPOs (Krigman et al. 1999). Persistent under pricing of IPOs could call into question the efficient market hypothesis for IPOs, however it does not per-se mean that the market for stocks with an established trading record is inefficient.

Stock Splits, like the 'January' effect may cast some doubt upon the efficient market hypothesis. Stock splits occur when the firm decides to split a single share into smaller bundles because the value of a single share has become unwieldy large. For example a firm whose share price has risen over time from 100 pence to 1500 pence may decide

to initiate a 15 for 1 stock split to return the price of any one share to a price which makes it easier for investors to trade. Given that the only thing that a stock split is nominally about is the resizing of a single share, then one should not expect an event effect as this act alone does not at face value offer new information about the future earnings potential of the firm. It has, however, been observed by numerous studies that not only do stock splits result in significant abnormal returns, but that these returns persist for up to a year. This is a period well beyond the short time that the market should require to assimilate new information into a firm's stock price, if stock splits do in fact convey new information about the earnings of a firm. Grinblatt, Masulis and Titman (1984) observed that Stock Splits result in short run abnormal returns. Inkenberry, Rankine and Stice (1996) observed from a sample of 1,275 stock splits between 1975 to 1990 that firms experience abnormal returns of 3.38%, with the smallest decal of firms experiencing abnormal returns of over 10%. Abnormal returns were found to persist for one year. Such persistent abnormal returns are explained as being due to a combination of signalling and trading effect. Signalling effects occur where the management anticipates a period of sustained improvement in profitability and signals this to the market via a stock split. Trading effects occur where a firm that has performed well over the past year engages in a stock split due to the rapid rise in its share price over the year, making the price of a single share unwieldy for bundling. The persistence of these abnormal returns may represent a challenge to efficient market hypothesis.

From the above whistle-stop tour of the event study literature three observations can be made. First, the use of the methodology is widespread in both the Strategy and Financial Economics literature. Second, event studies within and across the literatures, in common with other methodological tools, can yield both complementary and conflicting results. Third, there is a considerable body of research within the Financial Economics literature that casts some doubt on the underpinning assumption of the methodology, namely the efficient market hypothesis. Levis (1989) has found evidence that such anomalies in the efficiency of stock markets are not confined to the US, but also exist in the London Stock Exchange. It should, however, be noted that the existence of long run persistent abnormal returns and over, or under, reaction by the

market to specific events does not necessarily undermine the efficient market hypothesis or the usage of the event study methodology, both of which are still rigorously defended in the literature. An extensive literature review and critique by the founder of the method, Fama (1998), offers a compelling argument that the efficient market hypothesis is not undermined by studies observing long run abnormal returns (e.g. stock splits), or over-reaction to certain events (e.g. Initial Public Offerings). Fama argues that given that overreaction to announcements is found to be about as common as under reaction and that long run positive abnormal returns are found to be as common as long negative abnormal returns, that the core of the efficient market hypothesis is maintained, namely that anomalies should follow a random walk and thus their overall effect is cancelled out.

THEORY AND HYPOTHESIS

Mc Williams and Siegel (1997) launched a strong attack on the methodological rigour of event studies published in the management literature, arguing that many have failed to pay sufficient attention to establishing strong theoretic arguments as to why shareholder wealth should be affected by the events under study. Thus considerable attention is paid in this chapter to the expression of both the theoretical and empirical logic why announcements of alliances and progress in R&D should impact upon shareholder wealth as expressed in changes in share price. Six hypotheses are developed in this section. Support for the hypothesis is offered from the three case studies, Celltech, Oxford Molecular and PolyMASC, which form a part of this thesis and are presented in full in the appendices.

Alliances and Wealth Creation

In the literature five value enhancing benefits of inter-organisational co-operation are often cited. First, is the pursuit of economies of scale that may arise from the combination of two competing firms' activities into a single venture (Koh and Venkatraman, 1991). Second, alliances can facilitate access to complementary assets, which may not be contractually obtainable on the open market. Examples of

complementary assets include access to marketing and distribution channels. Glaister and Buckley (1997) undertook a survey of UK firms to discover what task and partner related characteristics most influenced firms in the selection of Joint Venture partners. They found that access to complementary assets was the second most important task related selection criterion. Their factor analysis finds access to complementary assets overall to be the third most important selection factor after access to technological know-how and financial assets. Important complementary assets for biotechnology firms include cash, due to their long time to market, complementary technology and access to channels of distribution, which are primarily controlled by large pharmaceutical firms. Hagedoorn (1993), in a study of the motives of 4,192 alliances, found that for the 847 biotechnology alliances in his sample 13% of them were primarily motivated by access to partner's financial resources, 35% for access to complementary technology, and 13% by market access issues. Thus 61% of biotechnology alliances were motivated by access to complementary resources and capabilities. Powell, Koput and Smith-Doerr (1996) in their study of collaborative networks between pharmaceutical and 225 biotechnology firms observed that the highest number of alliances by biotechnology firms involved access to key complementary resources: marketing channels and finance.

In the pharmaceuticals and biotechnology sector the breadth and fast moving nature of technological opportunities may explain the prevalence of alliances as tools to access complementary technological and commercial assets. Powell (1998) argues that the technological landscape in servicing an individual therapeutic area can be so large that even the largest pharmaceutical firms in the world cannot hope to contain complete technological resources under one vertically integrated structure argues it. Thus in seeking to make an impact in a given therapeutic area a pharmaceutical firm may pursue many different technological solutions at once through a network of partners who possess diverse technological capabilities which can be integrated into the pharmaceutical firm's complementary clinical trial management and marketing capabilities.

Third, alliances may be used to share costs, particularly in highly capital intensive sectors such as defence where Hagedoorn (1993) found 36% of alliances were motivated primarily by cost sharing. He found, however, that cost sharing was the primary motivating factor in only 1% of biotechnology alliances.

Fourth, alliances can be employed as a means of managing the risk, or uncertainty, surrounding investments in R&D. Management of risks such as technological and market lock-out can be powerful motives for alliance formation (Kogut, 1988). Uncertainties such as which technology will emerge as valuable and the risk of being locked out of the market by a competitor who shortens the time span for an innovation to get to market can be particularly important in sectors such as pharmaceuticals and biotechnology (Powell et al., 1996). Reduction of innovation time span is found by Hagedoorn (1993) to be a primary motive in 23% of alliances for 4,792 firms, with the importance for biotechnology firms rising to 31%. Winner take all games, or learning races where several firms are competing to obtain regulatory approval for a drug to be approved for use in treatment of the same illness, can be an important factor in pharmaceutical competition. Powell et al. (1996) have observed that biotechnology firms who ally with experienced (pharmaceutical) partners are more likely to succeed in learning races. It is widely understood that the first drug to obtain regulatory approval in the US obtains a dominant market share, while the next two drugs onto the market tend to make up the lion's share of the remaining market. This may explain the biotechnology sector findings of both Hagedoorn and Powell et al.

Fifth, alliances can be employed to jointly develop new capabilities or to acquire through learning knowledge that is of value to the firm, but cannot be obtained through an open market transaction. Theoretical papers have argued that alliances facilitate the transfer of tacit knowledge, which can be an important source of competitive advantage (Grant and Baden-Fuller, 1995; Kogut 1988). Learning and the transfer of tacit knowledge are also becoming an important focus of empirical research on the value of alliances. Powell et al. (1996) observed that pharmaceutical firms use alliances with biotechnology firms as a method of learning about new technologies to assess if the technology is sufficiently valuable to be absorbed into the vertically

integrated firm. Pisano (1990) empirically demonstrated that where a firm is more dependent on pharmaceuticals for its profits it is more likely to internalise promising biotechnology technologies. He noted that such technologies are often identified through alliance interaction with entrepreneurial biotechnology firms. Das et al. (1998) found strong support in their event study of 119 strategic alliances for the hypothesis that technological alliances are associated with greater abnormal returns than marketing alliances. It is argued that this is because technological alliances are normally between small innovative firms and large mature firms. The market views these as win-win alliances where access to complementary resources increases value, though learning opportunities may play a role. Doz (1996) observed from 3 alliance case studies, including one between pharmaceutical firms, that alliances where a high degree of learning took place were successful, while alliances that exhibited a low degree of learning were unsuccessful. There is a clear implication that higher degrees of learning lead to higher degrees of project success and hence higher value added.

Within the Celltech, Oxford Molecular and PolyMASC case studies (see appendices) there exists strong support for the contention that alliances are used for the purpose of access to complementary assets, cost sharing, management of risk and technological uncertainty, and learning new capabilities. Little evidence was found to support the argument that alliances were employed as means of obtaining economies of scale.

The example of Celltech, analysed in Chapter Three, illustrates the value adding potential of alliances in the UK biotechnology sector. The CEO of Celltech, Dr. Fellner, makes it clear in the Celltech case study that he views the management of inter-organisational collaboration with major pharmaceutical firms as being at the heart of his ambition to transform Celltech into a successful drug discovery and development company. From his perspective collaboration enables Celltech to share the risks and rewards of drug discovery and development in addition to enabling Celltech to have access to world class drug development capabilities, which would have been too costly and time consuming to independently create during its dramatic turnaround in the 1990s. As noted in Chapter Three, the underlying logic of collaboration at Celltech is summarised in the 1995 Annual Report as follows:

“Because of the high cost and complexity of world-wide product development and marketing the company collaborates with major pharmaceutical companies which possess the necessary technological expertise and financial resources to optimize the probability of success. As the company progresses towards profitability we intend to retain a greater proportion of European rights to new products” (Annual Report 1995)

Collaboration has brought Celltech several important benefits. The firm has obtained £26.5 million in milestone payments from alliance partners. It has conserved its scarce scientific and financial resources by passing development costs and activities onto partners. Dr. Yarranton, the firm’s Research Director, estimates that this has reduced the firm’s development costs by 50%, while also giving it access to world class clinical trial capabilities of leading pharmaceutical firms.

Executives at Celltech noted that collaboration has provided important learning benefits whereby the firm has learned the ability to manage development projects across organisational boundaries more efficiently and effectively than it could do so internally. This collaborative capability lies at the heart of the firm’s strategy. It has been learned slowly over time though collaborative ventures with several leading firms, including Bayer of Germany, Zeneca of the UK, and Merck of the USA. Executives in Celltech clearly believed that such collaborative capabilities add value to the firm. Supporting the arguments of these executives is the work of Gulati (1999). He conducts an analysis of 11 longitudinal case studies of alliances and argues that a collaborative capability is an important source of competitive advantage.

Another important capability has been extended and internalised through collaboration, namely management of drug development. It was noted by the CEO of the Celltech therapeutics that experience in the development of drugs, learned through collaboration with leading pharmaceutical firms between 1990 to 1997, now means that Celltech is able to manage more stages of the development process internally than it could in 1990. This he argued means that Celltech can now retain a greater proportion of the royalties to drugs created through collaboration than it could in 1990. This is because

before it could only bring discovery expertise to the partnership, thus partnership had to commence at the start of clinical trials. Now the firm can independently undertake the lower cost end of drug development, namely Phase I and II clinical trials and then enter into a collaboration with a firm who has expertise in Phase III trials and marketing. This means that Celltech can retain a greater proportion of final rights than it could before when entering into an alliance.

The theoretical benefit of a reduction in innovation time does not have appeared to have materialised, however, with Dr. Ney, Celltech's Development Director, noting that collaboration often means the firm must face a longer time to market. This she argues may be due to the slower speed of larger collaborators' decision making process, the time involved in knowledge transfer and differences in managerial control systems making co-ordination more difficult. All executives in the firm however noted that these costs were far exceeded by the benefits of collaboration outlined above. Thus it can be seen in the Celltech case that the primary value adding rationales of alliances are cost sharing, the management of technological uncertainty, access to complementary assets (drug development and marketing), and learning new organisational capabilities (drug discovery and management of collaboration).

The experience of PolyMASC dovetails with that of Celltech, despite the fact that Celltech is one of the oldest biotech firms in the sector, having been founded in 1980, while PolyMASC is quite young, having been formed in 1995. While Celltech collaborates primarily with large pharmaceutical firms, PolyMASC collaborative portfolio consists of small specialised biotechnology and pharmaceutical firms. It collaborates with partners for three explicit purposes. First, to share costs and gain access to complementary resources. The key complementary resource which PolyMASC seeks access to is Intellectual Property Rights. The technology of PolyMASC is a drug delivery mechanism known as PEGylation. This involves the coating of a drug to make delivery to the site of a disease easier. PolyMASC attaches the coating to other firm's drugs. Such combination of new a delivery mechanism with a drug currently on the market is required to enter clinical trials prior to marketing approval by regulators of the re-formulated compound. Thus collaboration with the

owners of the compound, who will be most knowledgeable on its clinical operation, is vital if PolyMASC products are to make it to the market. Second, PolyMASC uses alliances to enable the sale of its technology to other firms. This involves out-licensing the technology to other firms, however given the complexity of such knowledge transfer close collaborative links are required as opposed to a hands-off open market transaction. Having transferred the technology these firms then independently apply it to their own drug portfolio.

Given the high degrees of uncertainty attached to drug discovery and development, initially PolyMASC sought to confine itself to the licensing out of the drug delivery technology that had been transferred from the Royal Free Hospital to it upon its incorporation in 1995. Out Licensing is described as a low risk, low return strategy by the management. However in 1997 the firm choose to engage in strategic alliances which involved a third application of alliances, namely joint drug discovery and development through access to the drug discovery capabilities of other firms. Such alliances then involved the joint R&D of new drug compounds, which apply PolyMASC's drug delivery technology in new contexts. Thus in the PolyMASC's case one can observe that the key rationales behind alliance formation are cost sharing, access to complementary resources and capabilities, such as IP rights and drug development capabilities, and sharing the uncertainties of drug development.

Oxford Molecular exhibits the collaborative rationales of access to complementary resources and capabilities and learning. The objective of Oxford Molecular is not to engage in drug discovery or development on its own account, but rather to manage the drug discovery activities of other pharmaceutical and biotechnology firm's. As noted in the firm's web-site:

“The guiding principle for the Drug {Discovery} division is to build a bridge between successful university research projects and the needs of commercial research and development organisations involved in pharmaceutical and biotechnology R&D.” (Oxford Molecular, 1998).

According to Dr. David Ricketts, the head of Oxford Molecular's Drug Discovery Division, pharmaceutical firms engage in co-operative agreements with his division for three main reasons: to fill technological gaps; because they lack the time on their internal R&D timetable to research an issue; or to search for new technological opportunities. Filling technological gaps and search both involve Oxford Molecular obtaining access to technology and expertise that resides in universities and managing the process of either embedding that knowledge in a drug discovery project or transferring it from the university and into the pharmaceutical firm. These activities demonstrate two important rationales for alliances, namely, access to complementary capabilities that do not reside within the firm, and acquisition of new knowledge.

Three reasons why alliances may destroy value are proposed in the literature. The first is that the management of alliances incur costs of co-ordination (Koh and Venkatraman, 1991). Such costs can be tangibly observed in this thesis's case studies. Oxford Molecular engages in a time consuming process of weekly electronic updates between partners, monthly reviews, and quarterly face to face meetings. These reviews can, and regularly do, involve a re-appraisal of the objectives of the project, which can necessitate considerable re-organisation of resources within the project to facilitate new goals.

Second, there is a danger that alliances may be particularly vulnerable to 'theft' of the core competencies of one partner by the other (Bleeke and Ernst, 1991; Hamel, 1991), or other forms of opportunistic behaviour (Parke, Rosenthal and Chandran, 1993). It should, be noted, however, that recent empirical studies do not support the argument that alliances result in 'hollowing out' of core competencies through unbalanced learning (Mowery, Oxley and Silverman, 1996). Furthermore no evidence, either from interviewees or secondary sources, emerged from the Celltech, Oxford Molecular, or PolyMASC case studies to suggest that biotechnology firms feared, or had a propensity to engage in, 'hollowing out' of a partner's competencies.

Third, it has sometimes been argued through case evidence that alliances may be a prelude to a take-over (Bleeke and Ernst, 1991). This argument does not appear,

however, stand up in the face of large-scale empirical work. Hagedoorn and Sadowski (1999) analyse a sample of 6,425 inter-organisational relationships and found that only 2.4% of alliances transformed into joint ventures and that only 2.6% of alliances transformed into Mergers or Acquisitions. The fear that a small partner is vulnerable to take-over by a large partner appears to be unfounded with Hagedoorn and Sadowski (1999) observing that a smaller proportion of alliances between small and large partners are transformed into mergers or acquisitions than for large and medium sized partners. It was further observed that the probability of transformation was even lower in high technology sectors such as biotechnology. Finally, an event study of the shareholder wealth effects of 345 strategic alliances across multiple sectors by Chan et al. (1997) observed that in only five cases did the alliance transform into either an equity joint venture or a merger within a four year time horizon.

During 1999 there have been two mergers and acquisitions involving the three case firms from the appendices. Celltech took over a rival UK biotechnology firm, Chiroscience in 1999. PolyMASC was take-over in 1999 by Valentis, a NASDAQ listed US drug delivery company. In neither the case of Celltech and Chiroscience nor PolyMASC and Valentis had the two firms been alliance partners prior to the take-over announcement. Thus the argument that an alliance is a prelude to a take-over does not appear to be confirmed by either large-scale empirical studies or the case studies reported in the Appendices of this thesis.

From the above it can be reasonably argued that the value adding benefits of an alliance should outweigh the potential costs of partnership, thus one would anticipate a positive effect on shareholder wealth to accompany the announcement of an alliance. Furthermore, it should be noted that prior event studies, which have assessed the shareholder wealth effects of alliance and joint venture announcements, have all observed significant positive abnormal returns (Chan et al., 1997; Das et al., 1998; Koh and Venkatraman, 1991; Madhavan and Prescott, 1995; Mc Connel and Nantell, 1985).

From the above it can be predicted that for a UK biotechnology firm:

Hypothesis 1: announcement of an inter-organisational relationship, which has as a stated goal the combination of complementary assets, the management of technological uncertainty, the transfer between, or joint development of new capabilities or knowledge has a significant and positive effect on a firm's shares price performance.

Aside from the value adding benefits that collaboration can bestow through access to complementary resources and capabilities, the sharing of costs and uncertainty, and the acquisition of new capabilities via learning, alliances can play another very important role in the creation of value, namely, reputation building. Within the resource based view of the firm reputation is acknowledged as a potentially important source of competitive advantage (Grant, 1991; Hall, 1992), thus pursuit of increased reputation through alliance making can be a potentially valuable source of value. The underlying argument is that the greater the reputational resources of the firm the greater its ability to deliver value added, hence share price should rise if the firm experiences a rise in its reputational resources.

Empirical studies are increasingly exploring the value adding role that alliances play by transferring reputation from an established firm to a less experienced firm. Through a series of 7 case studies Larson (1992) observed that entrepreneurial firms often use alliances with high reputation, experienced, firms (which this thesis refers to as prestige alliance) as a way of breaking into an industry's 'inner circle'. Firms within the 'inner circle' had reputations for reliability, durability, and superior product quality, which can be important advantages in both the capital markets and in securing customers. Larson's cases demonstrated that entrepreneurial firms sought to enter the 'inner circle' through a series of stepwise alliances where the firm traded on the reputation of its alliance partners to acquire new, higher status, partners and over time enter the 'inner circle.'

Dollinger, Golden and Saxton (1997) undertook an experiment with MBA students where they were asked to select a joint venture partner. It was observed from the study that the decision to engage in a joint venture was significantly affected by the perceived reputation of the partner firm. The greater the perceived reputation of the firm the greater was its ability to attract partners. The fact that a partner was a competitor did not affect the student's decision to engage in a joint venture. From this study it can be concluded that decision makers clearly believe that the reputation of a firm is an important criterion in the selection of a partner. It should be noted, however, that the assumption that the behaviour of MBA students in a controlled experiment correlates with that of executives making real partnering decisions is somewhat dubious. Fortunately, there exists evidence in the UK that executives in firms are in fact strongly influenced by a partner firm's perceived reputation when choosing collaborative partners. Glaister and Buckley (1997) found in their survey that reputation was the third most important characteristic of a partner in the decision to partner, coming after trust between top management teams and the relatedness of a partner's business. Thus it can be concluded that not only does case evidence suggest that entrepreneurial firms believe that reputation of partners can add value, but also that firms in general are influenced by partner reputation in the decision to collaborate.

Based on a two-stage questionnaire survey of 98 firms, from seven countries, in the chemical sector Saxton (1997) observed that the relationship between the perceived financial, managerial and product quality reputation of an alliance partner is positively associated with the success of an alliance. Reputation was measured by managers involved in a given alliance on a ten-point scale, where one indicated that their partner had the worst reputation in the sector and ten indicated best in the sector. Performance of the alliance was measured both in terms of partner satisfaction with the alliance in general and also with its ability to deliver the goals for which it was founded. From this study one can see that managers in the chemicals sector (which included pharmaceutical firms) believe that the prior reputation has a positive effect on the outcome of an alliance. Thus it can be expected that the greater the prior reputation of an alliance the greater the probability that the alliance will be successful. The increased probability of success of a project undertaken with a higher reputation firm should be

recognised by the shareholder and thus announcement of such alliances should result in higher abnormal returns than announcement of alliances with lower reputation firms.

Clearly reputation plays an important role in the value added by collaborative partners in general, however, there exists evidence both within the literature and the case studies in this thesis that reputation has a particularly strong link with the performance of biotechnology firms. Stuart et al. (1999) analysed the relationship between alliance making, reputation building and both the speed and value of Initial Public Offering in 301 biotechnology firms in the US over a fourteen-year period. They concluded that the greater the reputation of the alliance partner network which a new biotechnology firm creates the faster it moves to IPO and the greater the value of the firm upon flotation.

They argue that alliances with high reputation firms should be positively associated with increased shareholder wealth because “(1) relationships have reciprocal effects on the reputations of those involved; (2) the evaluative capabilities of well known organisations are perceived to be strong; and (3) relationships with prominent organisations signal a new venture’s reliability, and thus its high likelihood of survival.” In other words shareholders in biotechnology firms will believe that if a high reputation pharmaceutical firm enters into an alliance with a biotechnology firm that it believes that the collaborative project has a good chance of success because failure will negatively impact on its wider reputation. Investors believe that the assessment of pharmaceutical firms counts because they have the necessary scientific and commercial capabilities to assess the likelihood of success in a drug R&D project. They also believe that these skills will be applied to a careful audit of the biotechnology firm’s proposition to avoid investing in a project that may negatively impact on the pharmaceutical firm’s reputation.

There is strong support for this line of reasoning in this thesis's case studies. Throughout the Celltech case there is a clear message from the management team that collaboration with leading pharmaceutical firms has a validating effect where by

shareholders value the judgement of such collaborators. Dr. Bloxham, the CEO of the therapeutics firm, made it clear that he believes that the Bayer alliance sent a strong signal to shareholders that when management said Celltech's drug development portfolio was valuable that this was not just hype, but backed up by the careful assessment of a highly reputed pharmaceutical firm. He clearly stated his belief that the announcement of an alliance with Bayer had a positive effect on Celltech's share price and that from this perspective the alliance was a success.

Bloxham's argument is supported by independent comments by an analyst in the Financial Times. Daniel Green, a respected observer of the UK biotechnology sector, commented that:

"Most importantly, Celltech has collaborations with big name drugs companies and their expert assessment is worth more than a City analyst's report. Where companies such as Merck, Bayer and Schering-Plough invest, others follow."
(Green 1994).

In the PolyMASC case there was again a strong believe that alliance partners acted as a validation of the value of the firm's technology and strategy in the eyes of shareholders. The Commercial Development Director was clear that in his view announcements of alliances had a positive effect on share price. In conversations he observed that he believed that alliance with a major pharmaceutical firm would have a very positive effect on the firm's share price, though it must be noted that at that time such an alliance had not been announced.

It can be seen that within both the literature and the case studies that there exists evidence that the reputation of an alliance partner is believed to have an impact on the assessment by shareholders of the future earnings potential of firms. This is because the reputation of alliance partners is associated with the probability of success of the projects the firm is undertaking and because high reputation (prestige) partners have access to both information and evaluative expertise that shareholders may lack. From the above it can be predicted that for a UK biotechnology firm:

Hypothesis 2: announcement of an inter-organisational relationship with a high reputation partner will have a greater positive effect on a firm's share price performance than an announcement of a partnership with firm with a lower reputation.

Progress in the R&D Process

At the heart of therapeutic biotechnology firms is the drive to gain regulatory approval for drugs, which they discover and develop either independently or in conjunction with collaborative partners. Drugs cannot be sold legally without extensive safety and efficacy testing. National regulators need to be convinced that the drug can be safely used and does in fact materially benefit the health of the targeted patient group before a drug can be marketed to the public either on prescription or over the counter. The drug development and approval process can be both costly and timely, being estimated to cost between \$200 and \$350 million to take a drug from discovery to marketing approval, and taking seven to twelve years to make it from concept to market (BIO, 1999). In return however, patented drugs obtain monopoly rights. Patent protection last for 17 to 20 years, thus giving biotechnology firms a 7 to 12 year monopoly right in the marketplace. Margins on patented drugs are very high, varying from 20% to 35%.

The drug approval process has four main stages. The first is pre-clinical trials, where promising compounds are identified. The second is clinical trials³⁵, where drugs pass through three stages referred to as Phase I, II and III clinical trials. The details of these trials have been outlined earlier in Chapter Three, however they are now briefly restated. Phase I trials seek to establish the safety of the drug on healthy volunteers. These trials represent about 11 per cent of the cost of performing clinical trials (Parexel International, 1996). Phase II trials involve establishing the tolerable range and most effective dosage on patients suffering the illness. Phase III trials involve further controlled tests where the efficacy and safety of the drug is compared relative to other

³⁵ For a more detailed description on what clinical trials involve the reader is referred to a layman's overview of the clinical trials process at <http://www.drkoop.com/hcr/trials/library.html>

treatments. Phase II trials represent about 27 per cent and Phase III trials about 62 per cent of the costs of the clinical trial process (Parexel International, 1996).

Exact figures on the average success rates of each stage of the clinical trials process are not available, however one can say that failure does occur at each stage³⁶. Thus it is reasonable to say that progress from one stage to a later one, for example from Phase I trials to Phase II, signals that the drug is moving closer to market approval. With progress from one stage to the next the uncertainty about the compound, in terms of its medicinal potential and likelihood of final approval, reduces. Thus one would expect a positive market reaction to announcements of progress in clinical trials.

Evidence that the market does in fact respond to announcements on the progress of clinical trials does exist. Using the event study methodology Torabzadeh, Woodruff and Sen (1998) analysed a sample of 204 announcements about FDA decisions to approve or reject New Drug Applications over the period 1981-1992. They observed that FDA approval lead to a two-day cumulative abnormal return of 1.13%. Rejection, which occurred in 20 cases, resulted in a negative abnormal return of 10.67%. Approval for the smallest quartile of the sample lead to the highest cumulative abnormal returns of 2.05%. All returns were significant at the 1% level.

More generally announcements about progress in R&D have been found to have an effect on shareholder wealth. Kelm et al. (1995) undertook an event study into shareholder wealth effects of 501 announcements regarding progress in the R&D process in 23 industries over the period 1977 to 1989. They observed that announcements about progress in R&D prior to product launch resulted in two-day cumulative abnormal returns of 0.88%, though the effect was much stronger in R&D intensive sectors such as biotechnology. For the 26 announcements about progress in the R&D process of biotechnology firms a two-day cumulative abnormal return of 6.64% was observed.

³⁶ Regulatory authorities and firms are not at present legally obliged to publicly release results of all clinical trials. Thus failed trials often go unreported. (drkoop, 1999).

Given the importance of progress along clinical trials in the drug approval process, and the more general empirical evidence on shareholder wealth effects of R&D announcements, it can be predicted that for a UK biotechnology firm:

Hypothesis 3: announcement of material progress in a firm's R&D process will have a significant and positive effect on that firm's share price performance. Material progress is taken as an announcement of pre-clinical trial results (discovery), entry into Phase I, II or III clinical trials and/or the successful completion of any such trials.

Given that progress from discovery (pre-clinical trials), to Phase I, to Phase II, to Phase III clinical trials demonstrates a reduction in medicinal and commercial uncertainty one would expect the announcement effect to be larger the further down the clinical trials process the drug gets and, hence, the closer is moves to regulatory marketing approval. As in the Chapter Three, the drug discovery process is split into two stages, discovery and Phase I clinical trials, which represent the process of knowledge Exploration, and Phase II and III clinical trials, which represent knowledge development, or Exploitation. It can be expected that shareholder wealth effects should be greater the further down the R&D process a drug moves. Thus it can be predicted that for a UK biotechnology firm:

Hypothesis 4: announcement of material progress in the development stage of a firm's R&D process in terms of clinical trial performance will have a greater positive effect than announcement of material progress in the discovery, or Exploration stage, of a firm's R&D process.

As noted above, prior empirical work in the literature indicates that significant and positive abnormal returns are associated with both announcements of alliances and progress in R&D. Prior studies have not, to the knowledge of this researcher, analysed the effects of these disparate events within a single sector. A reasonable argument can be put forward that one would expect that the overall impact of both forms of

announcement to be largely similar. Announcement about progress in clinical trials, as a whole, signal to the market reduction of uncertainty in the likelihood of any one drug reaching the marketplace. Such announcements do not, however, carry any information about the immediate financial rewards for the firm. Passing a clinical trial does not in of itself bring a direct financial reward. The regulator does not give the firm a financial prize for passing a trial. Alliances bring with them direct financial rewards in the form of milestone payments, cost sharing, or access to valuable resources and capabilities. Some bring with them signals to the shareholder that the likelihood of success of a project is high because the partner has conducted an audit of the project and is investing its financial capital and reputation in the project. However this signal is not necessarily as tangible and direct as a clear announcement that a project has passed a scientific hurdle set in a clinical trial, thus the uncertainty reduction signals of an alliance may be lower than those of clinical trials. From the above it can be argued that announcements of progress in clinical trials bring rich uncertainty reduction information, but no immediate financial rewards, while alliance announcements bring immediate and continuing financial rewards, but lower levels of uncertainty reduction information. Thus it can be predicted that for UK biotechnology firms:

Hypothesis 5: Announcement of an undifferentiated group of alliances (i.e. excluding reputation indicators) should have as positive an effect on share price performance as an undifferentiated group of announcements about clinical progress (i.e. excluding details of which stage of the R&D process the trial involves).

Hierarchy of Shareholder Wealth Effects: Appropriation, Development and Exploration

From the analysis of Celltech in Chapter Three it can be hypothesised that the further one moves along the continuum from knowledge Exploration to Exploitation the greater the financial feedback from the market should become (Levinthal and March, 1993; March 1991). From Chapter Three it was argued that prestige alliances are rich in both appropriation, through milestone payments and sharing of development costs,

and development information, through reduction in uncertainty over the likely success of an R&D project. Based on the theory outlined in Chapter Two and in-depth case research, in Chapter Three, it would be expected that announcements rich in both information about development and appropriation should be the most valuable as such announcements cover the full spectrum of Exploitation, which theory suggests to be more valuable in the marketplace than Exploration. Thus, it can be expected that announcements of Prestige Alliances should be very valuable.

Announcements about progress in Phase II or III clinical trials should be valuable because they offer information to the shareholder that the uncertainty about the success of the project has been reduced. Such announcements should be less valuable than Prestige alliances because they offer less information about Exploitation, offering information on reduction in development uncertainties but no immediate appropriation rewards via financial payments or reduced costs via transfer of development costs to partners.

Announcements of non-prestige alliance are valuable because they enable access to resources and capabilities, however they do offer uncertainty reduction signals to shareholders. Access to complementary assets can be viewed as aiding development and potentially offering milestone payments, however they do not offer uncertainty reduction signals to the market and therefore are less valuable signals of Exploitation than prestige alliances. They are also less valuable signals of Exploitation than Phase II/III trial announcements because, again, they do not offer uncertainty reduction signals to the market, while Phase II/III announcements do.

Announcements of discovery or Phase I clinical trial progress offer valuable insights to shareholders on the Exploration activities of the firm. Such announcements should therefore add value. The shareholder wealth effects of Exploration announcements should, however, be lower than Exploitation announcements, given the theoretically stated tendency of Exploitation to have more positive financial returns than Exploration activities (Levinthal and March, 1993; March, 1991). Thus it can be predicted that UK biotechnology firms:

Hypothesis 6: announcements, which are richer in appropriation information, should be associated with greater share price performance effects than deepening or Exploration announcements. Thus a hierarchy of announcement effects is expected, where the greatest effect comes from announcements of prestige alliances, followed by progress in Phase II/III clinical trials, regional alliances and discovery / Phase I progress.

METHODOLOGY

Event and Sample Definition

In this study of announcements by therapeutic biotechnology firms listed on the London Stock Exchange (LSE) and the Alternative Investment Market (AIM) that occurred between December 1995 and January 1999 was used. Announcements were obtained from three main sources: source company web-sites, Newswire services, accessed via *Reuters Business Briefings*, and the *Financial Times*. It is reasonable to expect that investors in any of these companies would have access to these three sources and thus the event information was deemed to have been released to the market the first day it appeared in any of these sources. Sources such as the *Financial Times* (Das et al., 1998) and the *Wall Street Journal* (Koh and Venkatram, 1991; Mc Connell and Nantell, 1985) are very commonly used in event studies. Usage of Newswire Services is less common (Chan et al., 1997), while this study is the first, to the best of this researcher's knowledge, to employ company web-sites as a source of announcements.

Over the period of the study 146 events were announced. In line with the recommendations of Mc Williams and Siegel (1997) a list of all 146 events in the sample can be found in Appendix Four of this thesis. These announcements were classified into four categories. The first event type was the announcement of a Prestige Alliance, which is used to indicate a high reputation alliance. Prestige alliances are recorded when the biotechnology firm enters into an alliance with a pharmaceutical firm which was ranked in the top 20 largest firms in terms of pharmaceuticals turnover

in 1998 (Firm, 1999). An example of a Prestige alliance in the sample was Peptide Therapeutics announcement of a new R&D Allergy vaccine alliance with pharmaceutical giant SmithKline Beecham on 10 February 1997. This announcement triggered a significant abnormal return of 11.24% on that day for Peptide Therapeutics. The second event type was alliances with any other firm, which were classified as Regional Alliances. An example of a Regional Alliance in the sample was PolyMASC's Blood Growth Factor drug discovery alliance with fellow UK biotechnology Oxford Molecular on 25 March 1998. This announcement triggered a significant abnormal return of 14.26% on that day for PolyMASC. Alliances are only classified as events where the announcement is of a new, as opposed to continuing, collaboration with a firm. Alliances were included in the sample if their stated purpose was joint drug Research and/or Development (e.g. Cantab Pharmaceuticals R&D alliance with Kakestsuke into a new Chickenpox and Shingles vaccine), licensing a compound to another firm in return for future royalties (e.g. Chiroscience's licensing of the local anaesthetic to Zeneca), or marketing and distribution (e.g. Cortecs marketing and distribution agreement for Macritonin in Greece with Glaxo-Wellcome).

The third event type was announcements about significant progress in pre-clinical drug discovery trials or Phase I clinical trials. An example of progress in pre-clinical drug discovery trials in the sample was Powderject's announcement on 16 September 1998 of positive results in a cancer vaccine trial on mice. This announcement triggered a significant positive abnormal return of 1.95% for Powderject. An example of a Phase I clinical trial announcement from the sample was Phytopharm's announcement on 13 October 1998 that its appetite suppressant drug had entered Phase I human clinical trials. This announcement triggered a significant and positive 4.48% abnormal return for Phytopharm.

The fourth event type was announcements about significant progress in Phase II or Phase III clinical trials. An example of progress in a Phase II clinical trial from the sample was KS Biomedica's announcement of positive results from its PII Rheumatoid Arthritis trial on 3 February 1998. This announcement triggered a

significant and positive abnormal return of 35.31% for KS Biomedix. An example of progress in a Phase III clinical trial in the sample was Phytopharm's announcement of positive Phase III eczema drug trials on 25 March 1998. This announcement triggered a significant and positive abnormal return of 15.30%.

Calculation of Actual, Normal and Abnormal Returns

The method by which abnormal returns were calculated and their significance tested followed the standard event study methodology as outlined by Mac Kinlay (1997) and Mc Williams and Siegel (1997). First actual returns for each company were calculated. Then a model of the firm's expected, or normal, share price performance behaviour was generated. The impact of an announced event upon the performance of the firm was then calculated as the difference between the actual performance of the share and its expected, or normal, behaviour. This difference is referred to as an abnormal return. The abnormal returns of each firm that experienced each category of event were averaged. The resulting average abnormal return was then tested to determine both its sign and whether it was significantly different from the null hypothesis of zero abnormal returns. In all cases it was found that announcement of a given category of event did, as hypothesised, have a positive and significant abnormal return. The method by which actual, normal, and abnormal returns were calculated is outlined below.

The actual return for a firm i is calculated as follows:

$$R_{it} = \log \frac{P_{it} + D_{it}}{P_{it-1}}$$

Where i = the company and t = day.

P_{it} = the share price of company i on day t .

D_{it} = the dividend granted for one share of company i on day t .

P_{it-1} = the share price of company i on day $t - 1$.

The expected, or normal returns, for company i are calculated as being a function of the returns obtained by the market where:

$$E_{it} = \alpha_i + \beta R_{mt} + \xi_{it}$$

R_{mt} = the continuously compounded realised returns on day t for a market index m .

α = the regression constant derived from regressing R_{it} against R_{mt} .

β_i = the regression coefficient derived from regressing R_{it} against R_{mt} .

ξ_{it} = is the error term derived from the regression with a mean of zero and a constant variance.

The values of α and β are derived from regressing R_{it} against R_{mt} over an estimation period starting at $t-180$ days prior to the event day $t=0$ and ending on day $t-20$. Following the advise of Mac Kinlay (1997) the estimation period was kept to a minimum of 120 days to enable good estimations of α and β . The estimation period terminates at day -20 to ensure that the event effect does not contaminate the estimation of the normal return model parameters.

In the case of 31 observations the firms had not been trading on the stock exchange for the 161 trading days required to generated estimates of α and β . This reduced the sample from a total of 146 events to 115 events. Following the advice of Mc Williams and Siegel (1997) for the benefit of future replication studies, details of the events excluded due to confounding events are found in Appendix Four.

It is an obvious point that the selection of market index strongly influences what the model will assign as the normal price behaviour of a given share. Most studies do choose a single index and do not test the sensitivity of the abnormal return effect to selection of market index. However, aware of recent criticisms of the event study method (Chatterjee, Lubatkin and Schulze, 1998), this study shall employ three market indices. The first model of normal returns regresses R_{it} against the returns of the FTSE All Share index. This assumes that the normality of the performance of a UK

biotechnology firm's share price is linked to the performance of the market as a whole. Thus

$$E_{it} = \alpha_i + \beta R_{FTSEAllt} + \xi_{it}$$

The second model regresses R_{it} against the returns of an index of all UK biotechnology firm's, referred to as UK Bio. This index was created specifically for this study, as no comprehensive market capitalisation weighted index of UK biotechnology stocks was publicly available. It is an index of all UK biotechnology firms listed on the London Stock Exchange and the Alternative Investment Market, weighted by market capitalisation. The base date for this index was December 1995. It was re-weighted every three months. If a new firm listed on either exchange during the three-month period then it was included in the index at the next re-weighting period. The UK Bio index was thus calculated as:

$$UKBIO_t = \frac{\sum_{i=1}^N R_{it} \otimes MktCapRatio}{N}$$

Where MktCapRatio, calculated for each firm included in the index once every three months, = $\frac{\text{Market Capitalisation of Firm}_i}{\sum_{i=1}^N \text{Market Capitalisation of Firm}_i}$

This model assumes that the normality of a UK biotechnology firm's share performance is primarily related to the performance of its peer group of UK biotechnology firms. Thus

$$E_{it} = \alpha_i + \beta R_{UKBIOt} + \xi_{it}$$

A third model regresses R_{it} against both the returns of the FTSE All Share index and the UK BIO index. This model assumes that the normal behaviour of a UK biotechnology share is a function both of the general performance of the stock market, moderated by the performance of its peer group of UK biotechnology firms. Thus

$$E_{it} = \alpha_i + \beta_1 R_{UKBIOt} + \beta_2 R_{UKBIOt} + \xi_{it}$$

A more simple, but important, mechanism by which the normal returns of a share can be modelled is to assume that the performance of the share in any given day should be equal to the average performance of the share over the estimation period. This assumes that the best guide to the normal behaviour of a share is its own historic performance rather than that of the market. Chatterjee et al. (1998) have called into serious question the use of market regression models in the estimation of the normal behaviour of shares and strongly recommend that when assessing the impact of an event upon share price both a market model and the more simple average adjusted returns model be employed. Mac Kinlay (1997) also recommends usage of such models in event studies. Thus normal behaviour is calculated as:

$$E_{it} = \frac{\sum_{t=-180}^{t=-20} R_{it}}{161}$$

Additionally, the impact that a simple adjustment by the market return, as opposed to a regression model, would have on the normal behaviour estimation was calculated. Thus normal share price behaviour was calculated as:

$$E_{it} = \frac{\sum_{t=-18}^{t=-20} R_{mt}}{161}$$

R_{mt} in one model was the FTSE All Share index, while in another it was the UK Bio index.

Abnormal returns are calculated to be the difference between actual returns and expected or normal returns.

$$AR_{it} = R_{it} - E_{it}$$

Where AR_{it} is the abnormal returns on day t for company i . It is expected that, in the absence of news impacting on the future earnings of the firm, abnormal returns should not on average be significantly different from zero. Consistent significant abnormal returns in the absence of the announcement of news impacting on the future earnings of a firm would run counter to the underlying premise of an efficient capital market.

For each event type the abnormal returns of all firms who experience such an event are averaged to produce an average abnormal return for the day AR_t .

$$AR_t = \frac{\sum_{i=1}^N AR_{it}}{N}$$

Where N = the number of firms in the sample who experience the given event.

It is found in the analysis that irrespective of the choice of model to calculate the normal, or expected, returns of a share all events continue to generate significant and positive abnormal returns. The abnormal returns generated by each of the above six models can vary by up to 2.2%.

Event Windows and Cumulating Abnormal Returns

On occasion it is appropriate to observe the cumulative effect of abnormal returns over a number of days. Cumulative returns, as opposed to the abnormal returns experienced on the event day zero, are tested in circumstances where the researcher has good reason to believe that the event effect should occur over an event window of greater than one day. This is appropriate where the researcher believes that either they may have mis-coded the event day or the market takes more than one trading day to assimilate the information into the share price. Cumulative Average Abnormal Returns were calculated as follows:

$$CAR_{t1, t2} = \sum_{t=t1}^{t=t2} AR_t$$

Under an efficient market hypothesis one would expect the market to take greater than one day to assimilate information into a firm's share price only where there is a leakage of that information to some actors into the market prior to the official announcement of the news to the market in general on day 0.

The null hypothesis of an event study is that both $AR_t = 0$ and $CAR_{t1, t2} = 0$. Two test statistics are applied to the hypothesis. A simple parametric student t test is calculated. Sample sizes of less than 120 reduce the power of parametric testing, thus in line with the suggestion of both Mac Kinlay (1997) and Mc Williams and Siegel (1997) a simple percentage positive negative test is also employed. The percentage positive negative has as its null hypothesis that share price will follow a random walk such that on any given trading day there is an equal probability that the share price of a given firm will be positive or negative. Therefore for an event effect to be observed in a sample of firms on average the number of positive returns reported would have to be either significantly above or below 50%. The use of both the parametric t-test and percentage positive negative tests together in one study is both prudent and accepted practice in the event study methodology (Chan et al., 1997; Koh and Venkatraman, 1991; Mac Kinlay, 1997; Mc Connell et al. 1985; Mc Williams and Siegel, 1997).

Mc Williams and Siegel (1997) note the validity and power of an event study is greatly reduced the longer the event horizon. They argue that studies should seek to accurately determine the date of the announcement, thus reducing the probability of pre-event abnormal returns due to mis-coding. Pre-event abnormal returns should, they argue, not occur in an efficient market. Mis-coding of the event day may occur where the researcher cannot determine with certainty the time at which the market received news of the event. In this research great care has been taken to accurately record the event day. Where possible the announced event has been obtained from the source company's web-site which normally records the date of the day on which a given announcement was given to the market. Where the event was announced during the hours of stock exchange trading that day was assigned as day 0. Where the date of announcement occurred after the hours of trading (as occurred in a number of cases)

the event day 0 was assigned as the next day of stock exchange trading, that being the first occasion on which the event news could be absorbed into the firm's share price. Where the date of the announcement could not be obtained from a firm's web-site it was obtained from Newswire services and *Financial Times* announcements listed in the *Reuters Business Briefings* database. Newswire service announcements would normally be delivered on the day of the announcement from the firm and directly into trading rooms, while *Financial Times* announcements tended to have a time lag of one day. Thus announcements obtained from Newswire services were coded as day 0 on the date the Newswire reported the event, while announcements in the *Financial Times*, were coded as the day prior to the publication of the news.

Table One, Panels A to D, summarises the average daily abnormal returns for the days -5 to +5 for each of the four event categories. Two models are included in these panels, the UK Bio market model, and the average adjusted return model. From Table One it can be seen the assumption that the event effect should be largely reflected on day 0 is confirmed. For Prestige Alliances no significant abnormal returns are observed outside day 0. For Phase II/III clinical trials gained the largest and most significant effect is observed on day 0 (significant at 1% level). Some small abnormal returns (significant at the 10% level) are observed using the non-parametric percentage positive negative test in days -3, -2, and -1, however these are not significant using parametric tests. Significant, though small effects are observed in day +2, at the 10% and 5% level. These results may be due to market re-examination of complex clinical trial test results over the period from day 0 to day 2. It could reasonably happen that an initial effect is observed on day 0 when the headline of the trial results is obtained, while a smaller secondary effect occurs on day 2 once the complex scientific details of the announcement have been fully analysed by investors. For Regional Alliances the majority of effects are confined to the event day 0 (significant at 1% level). Very small, but significant abnormal returns, of less than 1% are observed on days -3 and +3 at the 5% level. For Discovery and Phase I trials abnormal returns are observed in all days except -2, +1 and +5. These results may be questionable given the very small sample size of 8. Results outside day 0 are only significant at the 10% level while results on day 0 are significant at the 5% level.

INSERT TABLE ONE ABOUT HERE

The fact that abnormal return effects are largely confined to day 0 is in part due to the careful attention devoted to an accurate assessment of the event day 0. The results do support the contention that the effects observed are due to shareholders reaction to the information content in announcements of the four event categories rather than other information. This lends weight to the results detailed in the analysis section.

Control for Confounding Events

Another important threat to the validity of an event study's findings is the existence of confounding events (Mc Williams and Siegel, 1997). A confounding event is any announcement of information within, or around, the event window that may offer investors information on the future earnings potential of the firm. Thus the information effects of such an event would confound those of the events under study. Confounding events that occurred in this study included announcements of interim and year end results, progress in R&D, appointments of new senior managers, creation or termination of alliances, issue of new shares and acquisition of assets. An example of a confounding event in this sample was the announcement by Cortecs on 12 June 1998 of a new alliance with Boehringer Mannheim. On the same day Cortecs announced the resignation of its CEO. Even though abnormal returns were observed on this day, they could not be assigned wholly to the announcement of the new alliance. Thus the announcement of the resignation of the CEO acted as a confounding event to the announcement of a Prestige Alliance; hence this event was excluded from the sample of Prestige Alliances. Following the advice of Mc Williams and Siegel (1997), any confounding events observed within an eleven day window of -5 to +5 days were excluded from the study. 48 confounding events were observed, thus reducing the sample from 115 to 67 events. Following the advice of Mc Williams and Siegel (1997) for the benefit of future replication studies, details of the events excluded due to confounding events are found in Appendix Four.

It is commonly acknowledge that announcements regarding the success of firms tend to be published more frequently than failure (Torabzadeh et al., 1998). The frequency of announcements regarding the termination of alliances or failure of clinical trials was rare over the life of the sample. Only 6 announcements of alliance termination and 6 announcements of termination of clinical trails were observed. A sample size of 6 was considered to be too small to generate meaningful statistical test results and thus only announcements of success or progress are reported in this chapter. Thus the usable number of sample events is reduced from 67 to 55. From Appendix Four it can be seen that within this sample of 55 events there were 15 announcements of successful Prestige Alliances, 16 Regional Alliance, 16 Phase II/III clinical trials and 8 Discovery/Phase I clinical trials.

DATA ANALYSIS

Impact of Alliance Announcements upon Shareholder Wealth

Table Two reports the abnormal returns associated with the announcement of the formation of any form of alliance by a UK biotechnology firm over the period December 1995 to January 1999. This table reports the abnormal returns on the day of the announcement, day zero. As is standard practice in many event studies it also reports the cumulative abnormal returns in a number of event windows within an eleven-day event horizon from five days before the announced event to five days after the announcement. Abnormal returns are reported as percentages rounded up to two decimal places. Abnormal returns are reported from all six normal return models. Three market models are reported: the UK Bio index of all UK biotechnology firms, weighted by market capitalisation; the FTSE all Share index; and a combination of the FTSE All Share and UK Bio indices, referred to as the 2 Factor model. Three simple adjustment models are also reported: an Average Adjusted Returns model, adjusting actual returns by the average returns of the firm; UK Bio index adjusted returns; and FTSE All Share adjusted returns.

INSERT TABLE TWO ABOUT HERE

From Table Two it can be seen that all six models report highly positive returns to announcements of an alliance on day 0. Across all models the event effect for alliances was found to be significant at the 1% level using both a parametric test and the simple rank sign (percentage positive negative) test. This effect is largest for the Average Adjusted Returns model, with a return of 7.93%, significant at a 1% using both a standard parametric test and a percentage positive negative test. The smallest effect is reported by the UK Bio market model with an abnormal return of 7.48%. An F-test was used to determine if the returns generated by the six models differed significantly from each other. The f-statistic recorded was 0.1291 with a critical value of 2.2189. This indicates that the abnormal returns generated by each model are essentially drawn from the same sample and thus are not significantly different from each other. The f-statistic for the 31 individual company returns was 5.5487, with a critical value of 1.4653, indicating that the abnormal returns for individual firms were drawn, as one would expect, from different samples.

Significant cumulative abnormal returns continue to be generated by all models in all windows from days -5 to +5. Table One clearly illustrates that the full effect of the announcement of Prestige Alliances (Panel A), and the vast majority of the effect of announcements of Regional Alliances (Panel C), is captured on day zero. Thus it is reasonable to conclude that the shareholder wealth effects of announcement of alliances amount to a significant, positive, abnormal return of 7.74%. This percentage is the average of the abnormal return of all six models as reported the last row of Table Two.

Table Three reports the abnormal return effects for Prestige Alliances only. Significant abnormal returns are observed across all models for all event horizons. Table One, Panel A, shows that the only significant returns generated in a given day is on day zero, thus the full event effect is reflected in the first column of Table Three. All models generate abnormal returns on day zero significant at the 1% level both parametrically and using the percentage positive negative test. The largest event effect of 10.51% is generated using the FTSE All Share market model, while the smallest effect is 9.70%, generated by the FTSE All Share Adjusted returns model.

INSERT TABLE THREE ABOUT HERE

An F-test was used to determine if the returns generated by the six models differed significantly from each other. The f-statistic recorded was 0.0093 with a critical value of 3.0376. This indicates that the abnormal returns generated by each model are essentially drawn from the same sample and thus are not significantly different from each other. The f-statistic for the 15 individual company returns was 6.4562, with a critical value of 2.1014, indicating that the abnormal returns for individual firms were drawn, as one would expect, from different samples. Thus it can be said that the average event effect was an abnormal return of 10.04% (as reported in the last row of Table Three).

Table Four reports the abnormal return effects for Regional Alliances only. Significant abnormal returns are observed across all models for all event horizons, though in event horizons -2 to $+2$ through to -5 to $+5$ these effects are only significant at the 10% level for the FTSE All Share Adjusted returns model. It can be observed from Table One, Panel C, the largest and most significant abnormal returns are generated on the event day zero. Significant abnormal returns are generated on day -3 , of between $+0.41\%$ and -0.11% , and on day $+3$ the UK Bio model generates a small abnormal return of between $+0.88\%$ and $+0.99\%$. Relative to an average abnormal return of $+5.41\%$ generated across all 6 models, as reported in Table Four, the returns on days -3 and $+3$ are very small. Unlike announcements of clinical trial results where a possible logic for why the market would be slow to absorb information embedded in the announcement was offered in the methodology section, no logic has been put forward for the secondary effect on day $+3$ for Regional Alliances. It is, therefore, hard to justify a widening of the event horizon from one to seven days, given the diminished explanatory power that such an action would bring (Mc Williams and Siegel, 1997). Thus it can be reasonably argued that the vast majority of the event effect for Regional Alliances is captured on day zero. All models generate abnormal returns on day zero significant at the 1% level both parametrically and using the percentage positive negative test. The largest event effect of 5.70% is generated using the Average

Adjusted returns models, while the UK Bio market model generates the smallest effect of 5.05%.

INSERT TABLE FOUR ABOUT HERE

An F-test was used to determine if the returns generated by the six models differed significantly from each other. The f-statistic recorded was 0.2478 with a critical value of 3.0363. This indicates that the abnormal returns generated by each model are essentially drawn from the same sample and thus are not significantly different from each other. The f-statistic for the 16 individual company returns was 3.9464, with a critical value of 2.0572, indicating that the abnormal returns for individual firms were drawn, as one would expect, from different samples. Thus it can be said that the average event effect was an abnormal return of 5.41% (as reported in the last row of Table Four).

From the above analysis it is clear that there exists a strong and significant positive increase in shareholder wealth as a result of announcements of alliances. This effect is clearly stronger for announcement of higher reputation, Prestige Alliances than announcements of Regional Alliances. These results suggest that the uncertainty reduction signals that Prestige Alliances bring shareholders explain the considerable wealth effect difference between Regional and Prestige Alliances.

Impact of Announcements of Progress in R&D upon Shareholder Wealth

Table Five reports the abnormal returns generated by 24 announcements of progress in the R&D process of UK biotechnology firms. It can be seen that highly significant and positive abnormal returns are observed across all six models in the event horizon day 0 and days -1 to +1, -2 to +2. Significant returns are only obtained using both tests for the UK Bio Adjusted model in the horizons between event windows -3 to +3 through to -5 to +5. From Table One, Panels B and D, it can be seen that significant abnormal returns are observed for Phase II/III announcements between days -3, +3 and between days -4, +4 for Discovery/Phase I trial announcements. In the methodology section an argument was proposed as to why post-event day effects might be reasonably be

expected. There is a possibility that pre-announcement effects might be due to leakage of clinical trial results to selected investors. Such an occurrence did occur in the rather infamous whistle blowing incident at British Biotechnology where the head of Clinical Trials at the firm, concerned about the statements of senior management to the market, did divulge details of trials that were meant to remain secret to the investment community (Mc Namara, 1998).

INSERT TABLE FIVE ABOUT HERE

From Table Five it can be seen that the highest abnormal returns of 8.06% are generated by the FTSE All Share Adjusted returns model, while the lowest abnormal returns of 6.60% are generated by the 2 Factor model. While the returns generated by these two models differ by 1.46%, they are still both positive and substantial. The f-statistic recorded was 0.0439 with a critical value of 2.2203. This indicates that the abnormal returns generated by each model are essentially drawn from the same sample and thus are not significantly different from each other. The f-statistic for the 24 individual company returns was 6.5515, with a critical value of 1.5368, indicating that the abnormal returns for individual firms were drawn, as one would expect, from different samples. Thus it can be said that the average event effect was an abnormal return of 7.11% on day zero, rising to 9.57% between days -1 to +1 and 10.06% on days -2 to +2 (as reported in the last row of Table Five). All results are significant to at least the 2.5% level, however if the event horizon is widened to beyond -2 to +2, significance on the percentage positive negative test disappears in most cases, while is a low 10% in the remaining.

Table Six reports the shareholder wealth effects of announcements of progress in Phase II III clinical trials. Abnormal returns are positive and significant in all event horizons at a minimum of a 5% level, while for day zero all returns are significant at the 1% level, with the exception of the 2 factor model which is significant at the 2.5% level. The highest abnormal returns of 10.74% are generated by the FTSE All Share Adjusted model, while the lowest at 8.55% are generated by the UK Bio market model. Similarly, over the event horizon -2 to +2 the largest returns of 17.72% are generated

by FTSE All Share Adjusted model, while the lowest at 12.49% are generated by the UK Bio market model.

INSERT TABLE SIX ABOUT HERE

An F-test was used to determine if the returns generated by the six models differed significantly from each other. The f-statistic recorded was 0.0402 with a critical value of 3.0363. This indicates that the abnormal returns generated by each model are essentially drawn from the same sample and thus are not significantly different from each other. The f-statistic for the 16 individual company returns was 6.0688, with a critical value of 2.0572, indicating that the abnormal returns for individual firms were drawn, as one would expect, from different samples.

As noted earlier an argument could be made to consider an event horizon greater than day zero, given that event effects are observed in day +2 in Table One, Panel B, and a logical reason for their existence was proposed in the methodology. Average returns generated across all models for day zero were 9.32% and were significant at the 1% level. Cumulative abnormal returns in the period -2 to +2 are 14.11%, though the 5.23% difference between the lowest returns of 12.49% and the highest of 17.72% suggests that one should be cautious in using the average of the six models in periods outside day zero.

Table Seven reports the abnormal returns attributed to announcements of progress in Discovery (Pre-Clinical) and Phase I clinical trials. Weak abnormal returns are observed on day zero. It should be noted that given the very small sample size, 8 events, one cannot have much confidence in the precision of the parametric test, thus one should rely more on the simple percentage positive negative test (Mac Kinlay, 1997; Mc Williams and Siegel, 1997). Based on this test abnormal returns are found to be significant at the 5% level on day zero for the UK Bio models, at the 10% level for the 2 Factor and Average Adjusted Returns model, while no significant effects are observed using FTSE All Share models. Similarly weak effects are observed in the event horizons -1 to +1 and -2 to +2. From Table One, Panel D, it can be seen that weak event effects are observed using the percentage positive negative test on most

days from -4 +4, except on days -2, and +1. No cumulative abnormal effects are observed in Table Seven for any event horizon beyond -2 to +2. Looking at significance the most significant effects on day zero the highest abnormal returns of 2.81% are generated by the UK Bio adjusted model, while the smallest 2.74% are generated by the UK Bio market model (both significant at 5%). Over the period -1 to +1 the highest and lowest returns are +3.91% and +3.17% (significant at 5% and 10%), while over the period -2 to +2 abnormal returns become smaller with a high of +2.46% and a low of +1.75% (significant at the 10% level). The most significant returns are obtained in day zero, thus interpretation of the results is best confined to this horizon.

INSERT TABLE SEVEN ABOUT HERE

An F-test was used to determine if the returns generated by the six models differed significantly from each other. The f-statistic recorded was 0.0631 with a critical value of 3.0550. This indicates that the abnormal returns generated by each model are essentially drawn from the same sample and thus are not significantly different from each other. The f-statistic for the 8 individual company returns was 1.8398, with a critical value of 2.775, indicating that it cannot be said with confidence that the abnormal returns of individual firms were drawn from a different population. These results cast doubt on the power of this sample of events. Only returns, significant at a minimum of 5%, were averaged, giving an average abnormal return across the models of for day zero of 2.77%.

From the above analysis it is clear that there exists a strong and significant positive increase in shareholder wealth as a result of announcements of progress in R&D. The majority of this affect can be explained by Phase II/III clinical trials. It is difficult to say with a high degree of statistical confidence that the wealth effects of such trials are actually significantly greater than announcements of progress in Discovery and Phase I trials. This is because of the small sample size of Discovery/Phase I trial events. Based on this small sample it can, however, be suggested that there do appear to be larger wealth benefits from announcements of knowledge development, as represented by Phase II/III trials, relative to announcements of knowledge Exploration, as represented by Discovery/Phase I trial announcements. This would lend some weight to the theoretical

argument that Exploration could come to dominate over Exploitation due to greater financial returns.

Is there a Hierarchy of Shareholder Wealth Effects?

From the above analysis it is clear that there are strong shareholder wealth creation effects from the announcement of new alliances and progress in Phase II/III clinical trials. Weaker effects are observed for progress in Discovery (pre-clinical trials) and Phase I clinical trials. As has been argued above the majority of the effect is observed on the event day zero. Looking at Figure One, it can be visually observed that the effect of Prestige Alliances is larger than PII/III trials, followed by Regional Alliances and Discovery/Phase I trials. This supports the argument of hypothesis six that a hierarchy, based on Exploration and Exploitation, does exist and favours the greater Exploitation information content of Prestige Alliances over types of event.

INSERT FIGURE ONE ABOUT HERE

As argued above the effects attributable to Discovery and Phase I trials are less clear. To determine if a clear hierarchy exists between the three significant events a simple regression was employed. Abnormal returns for all events between -5 and +5 days were taken as the dependent variable and regressed against three independent dummy variables, namely Prestige Alliance, Regional Alliances and Phase II/III clinical trials on day 0. The results of this regression model are presented in Table Eight. This model yields an Adjusted R Square of 0.0507. Prestige Alliances have the highest coefficient, 0.07553, which is significant at the 5% level, while the Phase II/III dummy has a coefficient of 0.0666, which is significant at 7.5% level. Thus one can argue that Prestige Alliances have the greatest explanatory power, followed by Phase II/III clinical trials. This supports the argument that a hierarchy of announcements is present, as hypothesised.

INSERT TABLE EIGHT ABOUT HERE

ABSOLUTE CHANGE AS DISTINGUISHED FROM ABNORMAL RETURNS

This chapter has concentrated on calculation and analysis of abnormal returns as is normal in event studies. It is important, however, to note that abnormal returns are distinct from absolute changes in market capitalisation of the firm itself in response to a given event. Abnormal returns calculate the percentage return that an investor obtains over and above (or under as the case may be) that earned had the shareholder invested in a basket of other shares instead. Absolute changes in market capitalisation of the firm are calculated as the rise or fall in market capitalisation of a firm in response to a given event. That is:

$$\text{Absolute Change}_{\text{day } 0} = \text{Market Capitalisation}_{\text{day } 0} - \text{Market Capitalisation}_{\text{day } -1}$$

This informs the reader of the actual impact that an event had upon the company's valuation in absolute monetary value. For completeness and the general information of the reader absolute changes in market capitalisation on day zero were calculated for all events included in this chapter. These absolute changes in market capitalisation are provided in Tables Nine to Twelve. These tables provide the following details: type of event; name of the company who announced the event; percentage change in market capitalisation, for comparison the percentage mean absolute return across all models on day zero is also provided; finally the absolute change in market capitalisation in millions of pounds on day zero is listed. Table Nine provides information on Prestige alliances. Table Ten provides information on PII III clinical trials. Table Eleven gives the details of Regional Alliance events. Finally, Table Twelve provides details of Discovery and PI clinical trial events.

From Table Nine it can be seen that announcement of a Prestige Alliance partner generally adds several million pounds to a biotechnology firm's market capitalisation. The mean increase in market capitalisation was £ 12.3 million, with a maximum of £ 64.5 million and a minimum of a £ 8.9 million decline. Comparing the fourth and fifth columns indicates that the absolute change in market capitalisation mirrors the change in average percentage abnormal returns. The maximum difference between the two

percentages of 4.5% in the case of the strongly positive Powderject alliance with Glaxo-Wellcome.

Chiroscience achieved the largest increase in market capitalisation of £ 64.5 million when it announced that it entered into a marketing/licensing agreement with Zeneca for its newly approved local anaesthetic Chirocaine. This large increase in part compensated for the slightly negative earlier reaction by the market to Chiroscience's filing of the product for approval from the European Medical Agency. Table Ten indicates that *this announcement triggered a decline of £ 4.3 million* in Chiroscience's market capitalisation. At the time the market was worried about Chiroscience's ability to maximise its return on investment from the product due to lack of a strong marketing partner. As indicated in Chapter One, unfortunately for Chiroscience its agreement with Zeneca was short lived as it was forced to abandon the product to gain regulatory approval in its merger with Astra of Sweden. In March 1999 Zeneca and Chiroscience concluded an agreement to return Chirocaine to Chiroscience. In June 1999 Chiroscience announced that it had found new marketing partners, Purdue Pharmaceuticals in the US and Abbott Laboratories elsewhere (excluding Japan). On the same day Chiroscience announced that it would no longer be an independent company and merged with Celltech. The new group was called Celltech-Chiroscience. In November 1999 Celltech-Chiroscience announced a merger with Medeva. It was announced that the new company would revert to being called the Celltech Group. By January 2000 this new group was the fifth largest pharmaceutical firm by market capitalisation that had a primary listing on the London Stock Exchange³⁷. Celltech has emerged from the setbacks of the failure of its Septic Shock trials and its alliance with Bayer in May 1997, as outlined in the Celltech case study in Appendix One. It has to become one of the largest bio-pharmaceutical firms listed on the London Stock Exchange, while Chiroscience, which was the first UK biotechnology firm to gain regulatory approval of a novel therapeutic drug, has lost its name and independence.

³⁷ On 13 January 2000 Celltech had a market capitalisation of £ 1,081 million, while Medeva had a market capitalisation of £ 830 million. Only Glaxo-Wellcome, with a market capitalisation of £ 63,248 million, SmithKline Beecham (£44,424 million), AstraZeneca (£ 44,181 million) and Elan (£ 5,490 million) were larger than the Celltech Group.

INSERT TABLE NINE ABOUT HERE

From Table Ten it can be seen that announcements about PII/PIII clinical trials, in common with Prestige Alliances, generally coincide with increases in market capitalisation of several million pounds. The mean increase is £ 12.2 million, with a maximum increase of £ 74.3 million and a minimum of a £ 4.3 million decline (Chirocaine as discussed above). The £ 74.3 million increase is attributable to an Alzheimer's drug trial undertaken by Shire Pharmaceuticals. Alzheimer's is a severe condition that affects a large number of patients in the western world, who can live with the condition for many years. At present treatments are of limited effectiveness. If Shire were to succeed it would, thus, have a large and wealthy potential customer base. This may explain the large rise in market capitalisation.

INSERT TABLE TEN ABOUT HERE

From Table Eleven it can be seen that Regional Alliances attracted an almost uniformly positive rise in market capitalisation (in one case there was no change at all). As expected the change is smaller than for Prestige Alliances, however it still is in the order of a million or more pounds. The mean increase is £ 4.2 million, with a minimum of zero and a maximum of £ 16.1 million. This maximum was generated by Peptide Therapeutics alliance with Medeva in 1997. At the time Medeva was one of the largest biotechnology firms in the UK. The main feature of Regional Alliance announcements is that they have a positive and significant impact upon the firm's share price, but also that there is relatively less variability between firms than in the cases of Prestige Alliance and clinical trial announcements.

From Table Twelve it can be seen that on average announcements of Discovery and Phase I clinical trials attract a mean rise in market capitalisation of £ 6.3 million. This is higher than Regional Alliances, however the variation is much greater with a maximum of £ 30.5 million and a minimum of a £ 3.4 million decline. The largest rise of £ 30.5 million is attributable to results from a positive Phase I trial of its Hepagene hepatitis B vaccine treatment. The scale of the rise is somewhat surprising, given that only 2% of the estimated 350 million hepatitis B sufferers world-wide are in the most

lucrative markets of the US, EU and Japan (Pilling, 1998). The market may, however, have taken positive signals from the company's decision to scale up vaccine manufacturing facilities in preparation for approval of the drug and application for fast track drug trial status from the FDA as a positive signal.

INSERT TABLE ELEVEN ABOUT HERE

The second greatest rise was from Chiroscience's announcement of the results of PI trials of an MMP inhibitor. The target indication for the trials was cancer. Chiroscience's partner in this project was Bristol Meyers Squibb. The positive reaction at this early stage may have been for two reasons. First, MMPs were a relatively hot technology in 1998. British Biotech had attracted a great deal of attention with its research in MMPs. MMP inhibitors are believed to play a role in a wide variety of illnesses, in particular cancers and inflammation. Both of these are illnesses that affect a large portion of the population, and more importantly are common in western, high value, markets. Chiroscience's PI trials were to be in cancer. Importantly these trials were hoped to indicate that Chiroscience's second generation MMPs generated fewer side effects than earlier MMPs. Side effects can be a major cause of failure of drugs to gain regulatory approval.

The third greatest rise, of £ 6.1 million again related to a cancer drug, this time a vaccine from Powderject. This announcement came in a year when Powderject was attracting considerable positive attention in the stock market. Earlier in 1998 Powderject had signed a potentially large ten-year Prestige Alliance with Glaxo-Wellcome to research and develop vaccines. Potential milestones from this deal amounted to £ 180 million, coupled with a \$ 20 million equity investment by Glaxo-Wellcome.

INSERT TABLE TWELVE ABOUT HERE

Overall Tables Nine to Twelve offer some interesting information on the effects of individual announcements. Tables Nine and Eleven suggest that for this sample of firms, positive alliance announcements result in market capitalisation rising by several million pounds. Tables Ten and Twelve demonstrate that positive announcements of

clinical progress can result in large increases in market capitalisation at each stage. For example the results of Shire's PIII Alzheimer's trial resulted in a £ 74.3 million rise in market capitalisation; KS Biomedix's PII Rheumatoid Arthritis trial resulted in a rise of £ 28.4 million; while Medeva's PI hepatitis B trial coincided with a rise in the firm's market capitalisation of £ 30.5 million. From the above one can observe that in this sample of firms announcements of new alliances (prestige or regional) and of progress in all stages of clinical trials has the potential to add many millions to a firm's market capitalisation.

DISCUSSION AND CONCLUSIONS

It is clear from the analysis that **hypothesis one is strongly supported**. Shareholders of UK biotechnology firms attach significant importance to the formation of alliances. Announcement of an alliance adds 7.74% to a biotechnology company's market value (significant at the 1% level). Table Thirteen contrasts the findings of this study with those of the major event studies focusing on inter-organisational co-operative ventures in the literature. All except Reuter and Miller (1997) have reported positive returns, normally significant at the 1% level. The magnitude of the effect is much larger in the UK biotechnology sector than alliances as a whole. The largest effect reported in the studies in Table Thirteen is an average abnormal return on day zero of 3.54% for horizontal technological Strategic Alliances (Chan et al., 1997).

INSERT TABLE THIRTEEN ABOUT HERE

The findings of this chapter are not, however, surprising. Most studies focused on firms who would have had a track record of sales in final markets, however few of the firms in this chapter's sample have any significant sales volume and most have reported losses in the millions for several years. Biotechnology investments take years to come to market. Shareholders cannot therefore assess the performance of the firm in terms of current earnings and thus search for signals that the firm is both conserving scarce cash resources and making prudent investments that have a good chance of eventual marketing approval by regulators. Thus shareholders react positive to alliances which conserve cash resources by co-operative discovery and developing of

new drugs. The benefit is that their investment is concentrated in the highest value, aspect of the value chain, namely innovative discovery of new compounds. Alliances enable the firm to concentrate its investment in scientific discovery and access other firm's expensive development capabilities in alliances. PhARMA (1999) estimated that on average the development and marketing of a drug takes 8.9 years and consumes 53.5% of the total cost of bringing a drug to market. Thus co-development and marketing can conserve considerable resources, in addition to offering learning opportunities for young biotechnology firms in how to manage the development of a drug. Executives at Celltech noted that they had a very low investment in development (less than ten staff with no person dedicated to marketing) for the very reason that top quality development capabilities were very expensive to create internally but could be easily and cost effectively obtained via alliances.

Prior studies, as summarised in Table Thirteen, have not examined the effect of reputation of alliance partners upon abnormal returns. It is clear from the analysis section that **hypothesis two is strongly supported**. Prestige Alliances attract abnormal returns of 10.04%, while the effect of Regional Alliances is only about half that amount at 5.41% (both significant at the 1% level). The reasons to explain this result can be twofold. The first is that the resources and capabilities of a Prestige partner are likely to be significantly greater than a Regional partner, thus shareholders may believe that their firm can access superior development and marketing capabilities from Prestige partners. This would not only improve the quality of the drug development and marketing process relative to either going it alone or an alliance with a Regional partner, but would also potentially attract superior learning opportunities. For a smart firm, the logic goes, it is better to learn from the master of the craft. Comments by managers in the case companies suggest that the masters of drug development and marketing are Prestige Alliance partners.

The second benefit of Prestige Alliances is much more fundamentally about the knowledge Exploration and Exploitation process. Shareholders believe that Prestige Alliance partners have superior evaluative abilities to other partners. They have a long history of evaluating drug discovery and development projects. Their past judgement

on these matters have made them the leaders of one of the most profitable sectors in the world. They also have very considerable experience in alliances with biotechnology firms. It is not unusual for a pharmaceutical firm to have hundreds of alliances with biotechnology firms and universities going at once. Application of their evaluative abilities, coupled with prior experience of biotechnology alliances, to a decision to ally with a UK biotechnology firm is deeply valued by shareholders. Such an alliance signals to the biotechnology firm's shareholder that the best evaluators of the scientific risk versus financial benefit of a drug discovery and development projects have concluded that this is a project worth investing in. By investing the pharmaceutical firm's financial resources, via milestone payments, scarce and costly development capabilities, and most importantly their reputation in an alliance project, the biotechnology firm's shareholders' uncertainty about the likelihood of success in Exploration and development is greatly reduced. They also received immediate appropriation benefits, via milestone payments, in addition to reduced uncertainty about the likely future earnings potential of the project. This argument explains why Prestige Alliances are not only more valuable than Regional Alliances, but also experience the highest abnormal returns as predicted in **hypothesis six**.

It is clear from the analysis that **hypothesis three** is **strongly supported**. Announcements of progress in the R&D process attract abnormal returns of 7.11% (significant at the 1% level). This finding is in line with the findings of Kelm et al. (1995) who reported a 6.64% abnormal return associated with announcements of progress in the R&D process from a sample of 26 events. Shareholders clearly value such announcements because they reduce uncertainty about the likelihood of Exploration and development projects entering the appropriation phase, via marketing regulatory approval of a drug compound.

From the analysis section **medium support** for **hypothesis four** is observed. It is fair to say that the majority of the 7.11% effect observed in support of hypothesis three can be explained by announcements of progress in the development stage of the R&D process, classified in this thesis as Phase II/III clinical trials. These announcements are associated with an abnormal return of 9.32% (largely significant at the 1% level).

These announcements are of high value to the shareholder because they reduce the uncertainty about the success of development. The overall R&D process was found by PhARMA (1999) on average to take 15 years from discovery of a compound to sale in the marketplace, costing between \$200 and \$350 million (BIO, 1999). Development and marketing is estimated by PhARMA (1999) to represent over half the cost and length of time to complete the process. In the case of PolyMASC and more particularly Celltech it was made clear that the core value adding activity of the firm was the production of innovative novel drugs which make it through the regulatory process and on to the marketplace. As Dr. Fellner, CEO of Celltech, observed “the winners have to be the companies in therapeutic because the value added is so huge.”

This study is the first, to the best of this researcher’s knowledge, that attempts to assess the shareholder wealth implications of progress in the R&D process upon UK biotechnology firms in general. The findings confirm as a general rule, the observation of individual biotech managers, that announcements of progress in R&D drive improvements in shareholder wealth.

Due to small sample size, it is hard to say with confidence that Phase II/III clinical trial announcements are generally more valuable than Discovery/ Phase I trials. At a theoretical level one can say that it is expected that Discovery/Phase I trial announcements should be less valuable for two reasons. First, while they do lower the uncertainties faced by shareholders as to the likelihood of success in the R&D process their impact on uncertainty reduction is not as great as Phase II/III trials. At the end of the Discovery process all the shareholder knows is that testing on animals suggests that the compound may have a positive impact on human health. At the end of Phase I trials all that the shareholder knows is that the compound has a minimal level of safety in humans. Longer term effects and efficacy are only revealed via Phase II/III trials. Secondly, a lower effect would be expected because announcements of Discovery and Phase I trials are classified as Exploration activities. This is because according to Levinthal and March’s (1993) Exploration/Exploitation propositions the returns generated by Exploration activities should be lower than Exploitation. It is true to say that the abnormal returns from such announcements were low at 2.77% and only

significant at the 5% level. The evidence indicates that the shareholder wealth effects of Exploration are lower than development (Phase II/III trials). This lends **partial support to hypotheses four and six**, however, the small sample size of eight Discovery/Phase I events makes empirical generalisation problematic.

From the analysis **strong support for hypothesis five** is observed. The abnormal returns of Alliances at 7.74% are similar to those of announcements of progress in R&D at 7.11%. Both results are significant at the 1% level.. Widening the event window from day zero to an eleven day –5 to +5 day event horizon suggests that hypothesis five is confirmed. In the lead up to the to day zero the cumulative abnormal returns observed in Figure Two, are generally quite small, however on day zero both events have a very significant positive gain. The CAR from day –5 to day 0 is larger for all trials, however by day +5 the cumulative abnormal returns of both events have converged.

INSERT FIGURE TWO ABOUT HERE

Convergence can be reasonably expected to occur and largely confirms the beliefs of managers from the case studies. They attached a high importance to both alliances and progress in clinical trials. The activities are largely complementary. Most UK biotechnology firms seek to engage in independent discovery up to the point of patent and pre-clinical trials, but thereafter often engage in alliances to conserve resource on the one hand and on the other gain access to capabilities which increase the probability of eventual success. Two complementary resources and capabilities that are particularly important are access to complementary technology, as in the case of the Celltech-Bayer alliance expanded upon in the appendices, and complementary capabilities, such as development capabilities. Thus it makes sense that alliances be as valuable, in general, as progress in clinical trials. Progress in such trials is strongly affected by alliances, while alliances are driven by the aim of getting a project through clinical development and unto the market.

Based on both the analysis and the above discussion it can be seen that there exists **considerable evidence in support of hypothesis six**. From a financial perspective

Levinthal and March (1993) appear to be right. External markets do value Exploitation over Exploration. Table Fourteen summarises the abnormal returns generated by each event type in the context of the Exploration and Exploitation. This table summarises the abnormal return effects of each of the four categories of event and details the type of information each announcement offers the shareholder about Exploration and Exploitation. It can be seen that Prestige Alliances offer the most in terms of both information about Exploration and Exploitation and are thus the most valued. Prestige Alliances contain the richest information load providing insight for shareholders into appropriation (via uncertainty reduction, access to markets, and milestone payments), development (via cost sharing, access to complementary capabilities) and both Exploration and development (via the uncertainty reduction that their evaluative capabilities bestow and learning opportunities). Prestige Alliances generate an abnormal return of 10.04%.

INSERT TABLE FOURTEEN ABOUT HERE

Phase II/III clinical trials, bestow rich information about the development (Exploration) activities of the firm, playing a critical role in uncertainty reduction, and are thus the second most valuable announcement, generating an abnormal return of 9.32%. Regional Alliances generated the next highest returns of 5.41%, offering important information on the Exploration and development activities of the firm, via cost reduction, access to complementary capabilities, and learning opportunities. They do not, however, provide much uncertainty reduction information in contrast with either Prestige Alliances or Phase II/III clinical trials. The smallest, and least significant, returns were generated by announcements of Discovery or Phase I clinical trials. The results summarised in this table thus offer **strong support for hypothesis six.**

This chapter has explored the shareholder wealth effects of four announcements, linking these to the debate on Exploration and Exploitation, in addition to the central concerns of the biotechnology sector. Six hypotheses were developed, with all six finding support from the analysis of the data. It has been shown that in line with theoretical predictions in the literature the market does appear to value Exploitation

activities more than Exploitation. It has also been shown that the general impact that two events, namely alliance formation and progress in clinical trials, which managers in the sector believe to be important, do in general have a large positive and significant impact on shareholder wealth. Alliances and progress in R&D do add shareholder wealth within the UK biotechnology sector and the Exploration/Exploitation classification can offer insight into why value is created.

TABLE ONE: PERCENTAGE DAILY ABNORMAL RETURNS FOR ALL EVENTS

Panel A: Prestige Alliances (N=15)

Model	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4	Day +5
UK Bio											
Mean CAR	0.22	-0.03	-0.69	-0.56	-0.53	10.07	1.00	0.16	-0.56	0.56	0.95
Std Deviation	2.87	3.01	3.73	2.58	2.31	8.89	5.90	1.69	2.57	4.32	3.35
t-stat	0.3020	-0.0345	-0.7123	-0.8431	-0.4338	4.3839****	0.6559	0.3573	-0.8450	0.5048	1.0943
% Positive											
t-stat	1.2910	0.7746	-0.7746	0.2582	0.2582	3.3566****	0.7746	0.2582	0.2582	1.2910	0.2582
Average											
Returns Model											
Mean CAR	0.18	-0.19	-0.78	-0.43	-0.57	10.31	1.09	0.13	-0.70	0.76	0.98
Std Deviation	2.87	3.02	3.72	2.60	2.33	8.89	6.03	1.66	2.77	4.32	3.45
t-stat	0.2443	-0.2423	-0.8156	-0.6354	-0.9534	4.4892****	0.7009	0.3016	-0.9728	0.6783	1.0966
% Positive											
t-stat	0.7746	0.2582	-1.2910	0.2582	0.2582	3.3566****	0.7746	1.2910	0.7746	1.2910	0.7746

T stat significance for 1 tailed test: * p < .10 (>1.35); ** p < .05 (>1.76); *** p < .025 (2.14); **** p < .01 (>2.62).

Panel B: Phase II/III Trials (N=16)

Model	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4	Day +5
UK Bio											
Mean CAR	-0.55	-0.43	0.96	0.00	1.30	8.55	1.32	1.31	0.62	-1.82	0.26
Std Deviation	2.89	1.74	2.91	0.79	5.09	11.64	7.721	3.08	4.03	4.59	4.57
t-stat	-0.7582	-0.9916	1.3246	0.0215	1.0189	2.9382****	0.6845	1.7065*	0.6202	-1.5842	0.2275
% Positive											
t-stat	0.5000	-0.5000	1.5000*	0.5000	0.0000	3.0000****	-0.5000	1.5000*	2.0000**	-1.0000	-0.5000
Average											
Returns Model											
Mean CAR	-0.75	-0.51	1.25	0.19	1.22	9.40	1.56	1.42	0.56	-1.69	0.23
Std Deviation	2.89	2.11	3.26	0.90	5.18	11.24	7.61	3.03	4.12	4.76	4.90
t-stat	-1.0447	-0.9656	1.5387*	0.8611	0.9439	3.3540****	0.8191	1.8775**	0.5415	-1.4198	0.1916
% Positive											
t-stat	1.5000	0.0000	1.0000	1.5000*	1.5000*	2.5000****	-0.5000	2.0000**	2.5000****	-1.0000	0.5000

T stat significance for 1 tailed test: * p < .10 (>1.34); ** p < .05 (>1.75); *** p < .025 (2.13); **** p < .01 (>2.60).

Panel C: Regional Alliances (N=15)

Model	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4	Day +5
UK Bio											
Mean CAR	-0.35	0.72	0.41	-0.57	0.86	5.04	-0.29	0.37	0.88	0.09	0.72
Std Deviation	2.72	3.23	0.71	1.79	3.18	5.99	2.96	1.13	1.92	1.53	1.89
t-stat	-0.5211	0.8944	2.3182***	-1.2807	1.0842	3.3678****	-0.3934	1.3229	1.8290**	0.2530	1.5302
% Positive											
t-stat	-0.5000	0.5000	2.0000***	1.0000	1.0000	3.5000****	-0.5000	0.5000	2.5000***	1.0000	1.5000
Average											
Returns Model											
Mean CAR	-0.47	0.36	-0.11	-0.99	-0.5	5.70	-0.04	0.73	0.99	0.27	0.43
Std Deviation	3.19	3.55	1.55	2.19	6.21	5.81	2.88	1.00	2.12	1.55	2.00
t-stat	-0.5853	0.4070	-0.2896	-1.8010	-0.3223	3.9192****	-0.0628	2.9291	1.8870	0.6876	0.8673
% Positive											
t-stat	0.0000	1.5000*	2.0000**	1.0000	1.0000	4.0000****	0.6250	2.0000	2.0000	2.0000	0.5000

T stat significance for 1 tailed test: * p < .10 (>1.35); ** p < .05 (>1.76); *** p < 0.25 (2.14); **** p < .01 (>2.62).

Panel D: Discovery and Phase I Trials (N=8)

Model	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4	Day +5
UK Bio											
Mean CAR	0.46	-0.51	-2.30	-0.23	0.65	2.73	0.52	-1.41	-1.43	-0.41	0.82
Std Deviation	1.41	1.02	3.72	1.05	1.06	3.55	2.27	1.83	2.49	1.42	2.87
t-stat	0.9258	-1.4203*	-1.7474*	-0.6294	1.7295*	2.1776**	0.6490	-2.1778*	-1.6240*	-0.8148	0.8058
% Positive											
t-stat	0.7071	-0.7071	-0.7071	0.0000	1.4142*	2.1213**	0.7071	-1.4142	-2.1213	-1.4142*	0.0000
Average											
Returns Model											
Mean CAR	0.79	-0.47	-1.70	-0.24	0.65	2.76	0.33	-1.31	-1.35	-0.38	0.38
Std Deviation	1.45	1.11	2.22	1.06	1.32	3.63	2.49	1.85	2.47	0.89	3.34
t-stat	1.5383*	-1.1907	-2.1622**	-0.6421	1.3944	2.1516**	0.3700	-1.9963*	-1.5461	-1.2023	0.3223
% Positive											
t-stat	0.7071	0.0000	-1.4142*	0.0000	0.7071	1.4142*	0.0000	-1.4142*	-1.4142*	-1.4142*	0.0000

T stat significance for 1 tailed test: * p < .10 (>1.41); ** p < .05 (>1.89); *** p < 0.25 (2.36); **** p < .01 (>3.00).

TABLE TWO: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR ALL ALLIANCES (N=31)

Model	Day 0	Day -1 to +1	Day -2 to +2	Day -3 to +3	Day -4 to +4	Day -5 to +5
UK Bio						
Mean CAR	7.48	8.00	7.70	7.76	8.44	9.20
Std Dev	7.83	9.68	9.51	9.73	11.08	12.94
t-stat	5.3128****	4.5986****	4.5068****	4.4404****	4.2415****	3.9593****
% Positive						
t-stat	4.8493****	3.0533****	3.0533****	3.0533****	3.0533****	3.4125****
FTSE All share						
Mean CAR						
Std Dev	7.91	7.94	7.52	7.33	7.81	8.33
t-stat	7.74	10.31	10.39	11.29	12.49	14.23
% Positive	5.5699****	4.2879****	4.0301****	3.6143****	3.4220****	3.2591****
t-stat	4.8493****	3.0533****	3.0533****	2.6941****	2.3349****	2.3349****
2 Factor						
Mean CAR	7.76	7.78	7.27	7.16	7.79	8.48
Std Dev	7.66	10.15	10.25	11.01	12.05	13.94
t-stat	5.6388****	4.264****	3.9478****	3.6211****	3.5977****	3.3862****
% Positive						
t-stat	4.8493****	3.0533****	3.0533****	2.6941****	2.3349****	2.6941****
Avg Returns over Est. Window Adjusted						
Mean CAR	7.93	7.90	7.62	7.36	7.96	8.51
Std Dev	7.70	10.49	10.35	11.04	12.50	14.02
t-stat	5.7324****	4.1912****	4.1001****	3.7128****	3.5642****	3.3783****
% Positive						
t-stat	5.2085****	3.0533****	2.6940****	2.6940****	2.3349****	2.3349****
UK Bio Adjusted						
Mean CAR	7.86	7.69	7.27	6.87	7.33	7.73
Std Dev	7.76	10.79	10.87	11.78	13.39	15.14
t-stat	5.6370****	3.9670****	3.7242****	3.2468****	3.0473****	2.8429****
% Positive						
t-stat	5.2085****	2.6941****	2.6941****	2.6941****	2.3349****	2.6941****
FTSE All Share Adjusted						
Mean CAR	7.50	7.30	6.73	6.14	6.24	6.47
Std Dev	7.84	10.66	10.57	11.36	13.01	14.54
t-stat	5.3243****	3.8130****	3.5654****	3.0084****	2.6723****	2.4804****
% Positive						
t-stat	4.4901****	3.0533****	2.3349****	2.3349****	1.9756**	2.3349****
Average CAR across all models	7.74					

T stat significance for 1 Tailed test

* p <.10 (>1.31)

** p <.05 (>1.70)

*** p <.025 (>2.04)

**** p <.01 (>2.46)

TABLE THREE: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR PRESTIGE ALLIANCE (N=15)

Model	Day 0	Day -1 to +1	Day -2 to +2	Day -3 to +3	Day -4 to +4	Day -5 to +5
UK Bio						
Mean CAR	10.07	10.53	10.13	8.88	9.42	10.59
Std Dev	8.89	12.12	11.90	12.63	14.28	17.19
t-stat	4.3839****	3.3646****	3.2962****	2.7222****	2.5813***	2.3848***
% Positive						
t-stat	3.3566****	2.3238***	2.3238***	1.2910	1.2910	1.2910
FTSE All share						
Mean CAR						
Std Dev	10.51	11.13	10.61	9.16	9.65	10.57
t-stat	8.70	11.92	11.98	13.21	14.65	17.65
% Positive	4.6844****	3.6166****	3.4296****	2.6854****	2.5519***	2.3192***
t-stat	3.3566****	2.3238***	2.3238***	1.2910	0.7746	1.2910
2 Factor						
Mean CAR	10.45	11.14	10.54	9.25	9.72	10.69
Std Dev	8.56	11.77	11.82	12.95	14.52	17.54
t-stat	4.7299****	3.6642****	3.4537****	2.7666****	2.5937***	2.3606***
% Positive						
t-stat	3.3566****	2.3238***	2.3238***	1.2910	0.7746	1.29099
Avg Returns over Est. Window Adjusted						
Mean CAR	10.31	10.82	10.53	9.05	9.62	10.77
Std Dev	8.89	12.24	11.99	12.83	14.16	17.24
t-stat	4.4893****	3.4241****	3.4017****	2.7318****	2.6293****	2.4206***
% Positive						
t-stat	3.3566****	2.3238***	1.8074**	1.2910	1.2910	1.2910
UK Bio Adjusted						
Mean CAR	10.28	10.75	10.40	8.87	9.38	10.49
Std Dev	8.96	12.46	12.32	13.34	14.98	18.25
t-stat	4.4425****	3.3418****	3.2694****	2.5755***	2.4270***	2.2265***
% Positive						
t-stat	3.3566****	1.8074**	1.8074**	1.2910	1.2910	1.8074**
FTSE All Share Adjusted						
Mean CAR	9.70	10.43	10.07	8.45	8.55	9.62
Std Dev	9.25	12.28	11.87	12.79	14.60	17.58
t-stat	4.0622****	3.2896****	3.2862****	2.5604***	2.2690***	2.1195**
% Positive						
t-stat	2.8402****	2.3238***	1.8074**	1.8074**	1.8074**	1.8074**
Average CAR across all models	10.04					

T stat significance for 1 Tailed test

* p <.10 (>1.35)

** p <.05 (>1.76)

*** p <.025 (>2.14)

**** p <.01 (>2.62)

TABLE FOUR: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR REGIONAL ALLIANCE (N=16)

Model	Day 0	Day -1 to +1	Day -2 to +2	Day -3 to +3	Day -4 to +4	Day -5 to +5
UK Bio						
Mean CAR	5.05	5.62	5.42	6.71	7.53	7.90
Std Dev	5.99	6.15	6.11	6.16	7.58	7.42
t-stat	3.3678****	3.6542****	3.5506****	4.3558****	3.9721****	4.2570****
% Positive						
t-stat	3.5000****	2.0000**	2.0000**	3.0000****	3.0000****	3.5000****
FTSE All share						
Mean CAR						
Std Dev	5.48	4.95	4.63	5.61	6.08	6.23
t-stat	6.03	7.76	7.97	9.25	10.24	10.24
% Positive	3.6331****	2.5496***	2.3221***	2.4268***	2.3743***	2.4363***
t-stat	3.5000****	2.0000**	2.0000**	2.5000***	2.5000***	2.0000**
2 Factor						
Mean CAR	5.23	4.62	4.20	5.19	5.97	6.41
Std Dev	5.90	7.40	7.67	8.79	9.30	9.62
t-stat	3.5426****	2.4967***	2.1881***	2.3649***	2.5691***	2.6663****
% Positive						
t-stat	3.5000****	2.0000**	2.0000**	2.5000***	2.5000***	2.5000***
Avg Returns over Est. Window						
Adjusted Mean CAR	5.70	5.15	4.90	5.78	6.41	6.38
Std Dev	5.81	7.97	7.98	9.21	10.95	10.28
t-stat	3.9192****	2.5846***	2.4542***	2.5127***	2.3412***	2.4822***
% Positive						
t-stat	4.0000****	2.0000**	2.0000**	2.5000***	2.0000**	2.0000**
UK Bio Adjusted						
Mean CAR	5.58	4.81	4.34	5.00	5.40	5.14
Std Dev	5.84	8.35	8.70	10.19	11.87	11.52
t-stat	3.8262****	2.3064***	1.9943**	1.9612**	1.8189**	1.7848**
% Positive						
t-stat	4.0000****	2.0000**	2.0000**	2.5000***	2.0000***	2.0000**
FTSE All Share Adjusted						
Mean CAR	5.44	4.37	3.60	3.97	4.08	3.53
Std Dev	5.82	8.24	8.39	9.75	11.36	10.72
t-stat	3.7404****	2.1239**	1.7165**	1.6274*	1.4353*	1.3159
% Positive						
t-stat	3.5000****	2.0000**	1.5000*	1.5000*	1.0000	1.5000*
Average CAR across all models	5.41					

T stat significance for 1 Tailed test

* p < .10 (>1.34)

** p < .05 (>1.75)

*** p < .025 (>2.13)

**** p < .01 (>2.60)

**TABLE FIVE: PERCENTAGE CUMULATIVE ABNORMAL RETURNS:
DISCOVERY, PHASE I, II AND III TRIALS (N=24)**

Model	Day 0	Day -1 to +1	Day -2 to +2	Day -3 to +3	Day -4 to +4	Day -5 to +5
UK Bio						
Mean CAR	6.61	8.75	9.08	8.89	7.08	7.32
Std Dev	10.00	17.92	20.26	22.63	19.44	18.19
t-stat	3.2386****	2.3910***	2.1948***	1.9255**	1.7855**	1.9716**
% Positive						
t-stat	2.8577****	2.4495***	2.4495***	0.4082	0.4082	1.2247
FTSE All share						
Mean CAR						
Std Dev	6.97	9.21	9.73	9.98	8.41	8.09
t-stat	0.0992	17.68	20.15	22.38	18.83	17.53
% Positive	3.4411****	2.5517****	2.3654***	2.1846***	2.1887***	2.2607***
t-stat	2.4495***	2.8577****	2.4495***	0.8165	1.2247	1.2247
2 Factor						
Mean CAR	6.60	8.79	9.14	8.92	7.44	7.55
Std Dev	10.08	18.04	20.43	22.82	19.59	18.28
t-stat	3.2080****	2.3881***	2.1913***	1.9158**	1.8608**	2.0230**
% Positive						
t-stat	2.4495***	2.8577****	2.4495***	1.2247	1.2247	1.6330*
Avg Returns over Est. Window						
Adjusted Mean CAR	7.19	9.37	9.93	10.12	8.37	8.41
Std Dev	9.81	17.61	20.00	22.23	18.79	17.50
t-stat	3.5893****	2.6059****	2.4320***	2.2304***	2.1820***	2.3559***
% Positive						
t-stat	2.8578****	2.4495***	2.4495***	1.2247	1.2247	1.2247
UK Bio Adjusted						
Mean CAR	7.21	9.43	10.04	10.27	8.57	8.66
Std Dev	9.73	17.46	19.82	21.84	18.34	16.98
t-stat	3.6293****	2.6470****	2.4812***	2.3045***	2.2891***	2.4966***
% Positive						
t-stat	3.6742****	2.4495***	2.8577****	2.0412**	2.0412**	2.4495***
FTSE All Share Adjusted						
Mean CAR	8.06	11.88	12.44	12.64	9.89	9.27
Std Dev.	11.27	22.30	24.90	27.52	22.67	20.27
t-stat	3.5028****	2.6093****	2.4479***	2.2500***	2.1375***	2.2399***
% Positive						
t-stat	2.8577****	2.0412**	2.4495***	1.6330*	0.8165	1.6330*
Average CAR across all models	7.11					

T stat significance for 1 Tailed test

* p <.10 (>1.32)

** p <.05 (>1.71)

*** p <.025 (>2.07)

**** p <.01 (>2.50)

TABLE SIX: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR PHASE II AND III TRIALS (N=16)

Model	Day 0	Day -1 to +1	Day -2 to +2	Day -3 to +3	Day -4 to +4	Day -5 to +5
UK Bio						
Mean CAR	8.55	11.18	12.49	14.07	11.82	11.53
Std Dev	11.64	21.60	24.13	26.13	22.24	20.93
t-stat	2.9384****	2.0675**	2.0702**	2.1542***	2.1267**	2.2046***
% Positive						
t-stat	3.0000****	2.0000**	2.5000***	3.0000****	3.0000****	2.5000***
FTSE All share						
Mean CAR	9.25	12.23	13.97	15.82	13.75	13.03
Std Dev	11.34	21.02	23.51	25.40	21.00	19.62
t-stat	3.2645****	2.3265***	2.3768***	2.4911***	2.6192****	2.6562****
% Positive						
t-stat	2.5000***	2.5000***	2.5000***	2.5000***	3.0000****	3.0000****
2 Factor						
Mean CAR	8.60	11.41	12.84	14.32	12.46	12.22
Std Dev	11.69	21.70	24.22	26.23	22.21	20.77
t-stat	2.9425****	2.1023**	2.1204**	2.1846***	2.2439***	2.3535***
% Positive						
t-stat	2.0000**	2.5000***	2.0000**	2.0000**	2.0000**	2.0000**
Avg Returns over Est. Window						
Adjusted						
Mean CAR	9.40	12.18	13.80	15.61	13.41	12.89
Std Dev	11.21	20.97	23.50	25.43	21.19	19.80
t-stat	3.3540****	2.3243***	2.3494***	2.4553***	2.5316***	2.6045****
% Positive						
t-stat	2.5000***	2.0000**	2.5000***	2.5000***	2.5000**	2.0000**
UK Bio Adjusted						
Mean CAR	9.41	12.20	13.83	15.65	13.46	12.95
Std Dev	11.13	20.78	23.26	24.95	20.61	19.13
t-stat	3.3814****	2.3491***	2.3783***	2.5089***	2.6123****	2.7086****
% Positive						
t-stat	3.0000****	2.0000**	2.5000***	3.0000****	3.0000****	2.5000**
FTSE All Share Adjusted						
Mean CAR	10.74	16.04	17.72	19.61	15.98	14.52
Std Dev	12.87	26.40	29.12	31.47	25.64	22.89
t-stat	3.3376****	2.4317***	2.4356***	2.4927***	2.4927***	2.5366***
% Positive						
t-stat	3.0000****	2.0000**	2.5000***	2.0000**	2.0000**	2.0000**
Average CAR across all models	9.32	12.54	14.11			

T stat significance for 1 Tailed test

* p <.10 (>1.34)

** p <.05 (>1.75)

*** p <.025 (>2.13)

**** p <.01 (>2.60)

TABLE SEVEN: PERCENTAGE CUMULATIVE ABNORMAL RETURNS FOR DISCOVERY AND PHASE I TRIALS (N=8)

Model	Day 0	Day -1 to +1	Day -2 to +2	Day -3 to +3	Day -4 to +4	Day -5 to +5
UK Bio						
Mean CAR	2.74	3.91	2.26	-0.0147	-0.0239	-1.11
Std Dev	3.55	3.86	4.68	-0.1173	0.0529	5.15
t-stat	2.1776**	2.8638***	1.3662	-0.7007	-1.2767	-0.6096
% Positive						
t-stat	2.1213**	2.1213**	2.1213**	-1.4142	-1.4142	0.0000
FTSE All share						
Mean CAR	2.41	3.17	1.25	-1.70	-2.26	-1.79
Std Dev	3.52	4.17	5.16	5.39	4.95	4.20
t-stat	1.9334**	2.1505**	0.6854	-0.8913	-1.2922	-1.2031
% Positive						
t-stat	0.7071	1.4142*	0.7071	-2.1213	-2.1213	-2.1213
2 Factor						
Mean CAR	2.59	3.57	1.75	-1.88	-2.59	-1.80
Std Dev	3.64	3.63	4.64	6.05	5.65	4.86
t-stat	2.0167**	2.7806***	1.0639	-0.8785	-1.2964	-1.0457
% Positive						
t-stat	1.4142*	2.1213**	1.4142*	-0.7071	-0.7071	-0.7071
Avg Returns over Est. Window Adjusted						
Mean CAR	2.76	3.74	2.19	-0.86	-1.71	-0.54
Std Dev	3.63	4.76	5.36	5.54	4.90	5.31
t-stat	2.1517**	2.2216**	1.1534	-0.4402	-0.9864	-0.2886
% Positive						
t-stat	1.4142*	1.4142*	0.7071	-1.4142	-1.4142	-0.7071
UK Bio Adjusted						
Mean CAR	2.81	3.90	2.46	-0.48	-1.21	0.06
Std Dev	3.56	4.95	5.80	5.94	5.53	6.10
t-stat	2.2375**	2.2315**	1.2014	-0.2267	-0.6218	0.0291
% Positive						
t-stat	2.1213**	1.4142*	1.4142*	-0.7071	-0.7071	0.7071
FTSE All Share Adjusted						
Mean CAR	2.70	3.55	1.87	-1.30	-2.28	-1.23
Std Dev.	3.61	4.77	5.44	5.76	5.16	6.14
t-stat	2.1110**	2.1010**	0.9734	-0.6388	-1.2483	-0.5683
% Positive						
t-stat	0.7071	0.7071	0.7071	0.0000	-1.4142	0.0000
Average CAR across models with a significance of at least 5%	2.77					

T stat significance for 1 Tailed test

* p < .10 (>1.41)

** p < .05 (>1.89)

*** p < .025 (>2.36)

**** p < .01 (>3.00)

TABLE EIGHT: RESULTS OF DUMMY REGRESSION MODEL

	Coefficient	Standard Error	T statistic	P-value
Intercept	0.0267	0.0299	0.8919	0.3766
Prestige Alliance	0.0755	0.0370	2.0398	0.0466
PII/III trials	0.0666	0.0366	1.8181	0.0749
Regional Alliance	0.0274	0.0366	0.7496	0.4569
R Square	0.1034			
Adjusted R Square	0.0507			
Observations	55			

TABLE NINE: ABSOLUTE CHANGE IN MARKET CAPITALISATION FOR PRESTIGE ALLIANCES (DAY 0 LESS DAY -1)

Biotechnology Company Name	Pharmaceutical Alliance Partner	Principal purpose of alliance	% Change in Market Cap.	Average Percentage Abnormal Returns	Absolute Change in £ millions
Chiroscience	Schering Plough	R&D	+ 7.4	+ 6.3	+ 18.6
Chiroscience	Bristol Meyer Squibb	R&D	+ 1.7	+ 2.1	+ 4.8
Chiroscience	Zeneca	Licence of drug to Zeneca	+ 22.8	+ 20.3	+ 64.5
Cortecs	Astra	Distribution agreement	- 3.5	- 2.9	- 8.9
Cortecs	Glaxo-Wellcome	Distribution agreement	+ 0.0	+ 0.1	+ 0.0
KS Biomedix	Hoffman La Roche	R&D	+ 6.3	+ 6.18	+ 2.5
Oxford Biomedica	Rhone-Ploulenc-Rorer	R&D	+ 16.7	+ 14.6	+ 1.7
Oxford Biomedica	Rhone-Ploulenc-Rorer	R&D (different alliance to one above)	+ 23.1	+ 21.0	+ 2.6
Peptide Therapeutics	SmithKline Beecham	R&D	+ 12.2	+ 11.2	+ 13.6
Peptide Therapeutics	Pfizer	R&D	+ 3.8	+ 3.1	+ 3.6
Peptide Therapeutics	Novartis	R&D	+ 2.0	+ 2.3	+ 0.7
Phytopharm	Pfizer	R&D	+ 11.6	+ 10.4	+ 4.2
Powderject	Glaxo-Wellcome	R&D	+ 33.1	+ 28.6	+ 61.5
Shield Diagnostics	Abbot Laboratories	R&D	+ 23.8	+ 14.3	+ 15.4
Xenova	Eli Lilly	R&D	+ 16.0	+ 17.6	+ 7.3
All Prestige Alliances:					
Mean			+ 11.8	+ 10.3	+ 12.3
Median			+ 11.6	+ 10.4	+ 4.2
Std Deviation			10.6	9.0	21.5
Maximum			+ 33.1	+ 28.6	+ 64.5
Minimum			- 3.5	- 2.9	- 8.9

TABLE TEN: ABSOLUTE CHANGE IN MARKET CAPITALISATION FOR PII/III CLINICAL TRIALS (DAY 0 LESS DAY -1)

Biotechnology Company Name	Stage of Trial	% Change in Market Cap.	Average Percentage Abnormal Returns	Absolute Change in £ millions
Biocompatibles	PIII EMA filing	+ 6.6	+ 5.6	+ 22.2
Chiroscience	PIII EMA filing	- 1.6	- 2.0	- 4.3
Cortecs	PIII launch of diagnostic	+ 9.2	+ 8.3	+ 22.3
KS Biomedix	PII results	+ 42.3	+ 35.3	+ 28.4
Peptide Therapeutics	PII enters	+ 7.8	+ 7.3	+ 9.3
Phytopharm	PII results	+ 12.3	+ 15.3	+ 3.2
Phytopharm	PII enters	+ 2.3	+ 2.5	+ 0.6
Proteus International	PIII Approval (of a diagnostic)	+ 42.0	+ 35.5	+ 9.4
Scotia Holdings	PII results	+ 0.7	+ 1.1	+ 3.1
Scotia Holdings	PIII EMA filing	+ 2.8	+ 3.2	+ 8.5
Shield Diagnostics	PIII launch of diagnostic	- 1.1	- 1.6	- 1.5
Shield Diagnostics	PIII FDA Approval (of a diagnostic)	+ 7.9	+ 4.9	+ 7.5
Shield Diagnostics	PIII FDA filing	+ 9.9	+ 9.0	+ 9.0
Shire Pharmaceuticals	PIII results	+ 0.1	- 0.2	+ 0.7
Shire Pharmaceuticals	PIII results	+ 10.9	+ 9.9	+ 74.3
Stanford Rook	PIII enter	+ 15.5	+ 14.6	+ 2.2
All PII/III				
Mean		+ 10.5	+ 9.3	+ 12.2
Median		+ 7.8	+ 6.5	+ 8.0
Std Deviation		13.3	11.4	18.9
Maximum		+ 42.3	+ 35.5	+74.3
Minimum		- 1.6	- 2.0	- 4.3

TABLE ELEVEN: ABSOLUTE CHANGE IN MARKET CAPITALISATION FOR REGIONAL ALLIANCES (DAY 0 LESS DAY -1)

Biotechnology Company Name	Alliance Partner	Principal purpose of alliance	% Change in Market Cap.	Average Percentage Abnormal Returns	Absolute Change in £ millions
Cambridge Antibody	Progenitor	R&D	+ 1.0	+ 1.9	+ 0.9
Cantab Pharmaceuticals	Marie Curie Cancer Care	R&D	+ 3.2	+ 2.9	+ 4.3
Cantab Pharmaceuticals	Kakestsuke	R&D	+ 2.4	+ 2.6	+ 2.5
Celsis International	Becon Dickinson	Distribution agreement	+ 0.0	+ 0.0	+ 0.0
Celltech	Zymogenetic	R&D	+ 3.1	+ 2.8	+ 7.6
Chiroscience	Alcon Laboratories	R&D	+ 1.9	+ 1.5	+ 7.4
Chiroscience	Geron	R&D	+ 1.9	+ 1.8	+ 5.3
Peptide Therapeutics	Medeva	R&D	+ 19.7	+ 17.7	+ 16.1
Peptide Therapeutics	OraVax	R&D	+ 3.6	+ 3.4	+ 3.6
PolyMASC	Oxford Molecular	R&D	+ 16.0	+ 14.3	+ 3.8
PolyMASC	Traskaryoic Therapeutics	R&D	+ 7.7	+ 7.5	+ 1.8
Shield Diagnostics	Hitachi Chemical	Distribution agreement	+ 1.4	+ 0.1	+ 1.0
Therapeutic Antibodies	Altana	License of product from Altana	+ 4.8	+ 4.9	+ 2.3
Vanguard Medica	Elan	License of product to Elan	+ 5.0	+ 4.5	+ 2.4
Xenova	Wallac	R&D	+ 2.9	+ 3.7	+ 1.2
Xenova	Institute of Grassland	R&D	+ 18.6	+ 17.6	+ 6.3
All Regional Alliances:					
Mean			+ 5.8	+ 5.5	+ 4.2
Median			+ 3.1	+ 3.2	+ 3.0
Std Deviation			6.4	5.8	3.9
Maximum			+ 19.7	+ 17.7	+ 16.1
Minimum			+ 0.0	+ 0.0	+ 0.0

TABLE TWELVE: ABSOLUTE CHANGE IN MARKET CAPITALISATION FOR DISCOVERY AND PI CLINICAL TRIALS (DAY 0 LESS DAY -1)

Biotechnology Company Name	Stage of Trial	% Change in Market Cap.	Average Percentage Abnormal Returns	Absolute Change in £ millions
Cambridge Antibodies	PI enters	+ 0.8	+ 1.0	+ 0.6
Chiroscience	PI enters	- 1.0	- 1.3	- 3.4
Chiroscience	PI enters	+ 6.3	+ 6.0	+ 15.0
Medeva	PI results	+ 9.7	+ 9.2	+ 30.5
Oxford Biomedica	PI enters	+ 0.0	+ 0.0	+ 0.0
Phytopharm	PI enters	+ 4.5	+ 4.5	+ 1.5
Proteus International	PI results	+ 0.0	- 0.0	+ 0.0
Powderject	Pre-clinical positive results	+ 2.3	+ 1.9	+ 6.1
All Discovery/PI				
Mean		+ 2.8	+ 2.7	+ 6.3
Median		+ 1.6	+ 1.5	+ 1.1
Std Deviation		3.7	3.6	11.3
Maximum		+ 9.7	+ 9.2	+ 30.5
Minimum		- 1.0	- 1.3	- 3.4

TABLE THIRTEEN: SUMMARY OF PAST FVINT STUDIES OF JOINT VENTURES AND ALLIANCES

Paper	Chan et al, 1997	Das, Sen and Sengupta, 1998	Koh and Venkatraman, 1991	Madhavan and Prescott, 1995	McConnell and Nantell, 1985	Reuter and Miller 1997	Mc Namara 1999
Published in	Journal of Financial Economics	Academy of Management Journal	Academy of Management Journal	Academy of Management Journal	The Journal of Finance	Strategic Management Journal	N/A
Event type	<i>Strategic Alliances</i> where neither an equity Joint Venture is formed, nor do partners purchase shares in each other.	<i>Strategic Alliances</i> which are contractual combination of resources not involving equity participation.	<i>Joint Ventures</i> (not defined).	<i>Joint Venture</i> involving equity participant between 2 or more firms, or on-going manufacturing and marketing.	<i>Joint Ventures</i> involving the combination of some resources of two firms under joint management.	<i>International Joint Ventures</i> where the US partner buys out the other partner's equity	Strategic Alliances involving pooling of resources or capabilities by 2 firms.
Number of 'events	345 Strategic alliances by 460 firms.	119 Strategic alliances.	175 Joint Ventures involving 275 firms.	108 Joint Ventures	136 Joint Ventures involving 210 firms.	75 US International Joint Ventures.	31 Alliances involving 44 firms.
Event effects	Day 0 Abnormal returns for all Strategic Alliances (SA) = 0.64% at $p < .01$. Horizontal, Technology SA AR = 3.54% at $p > .01$. Non-horizontal, non technology SA AR = 1.45 % at $p < .01$. All other Strategic alliance formations not statistically significant.	For all Strategic Alliances (SA) Day 1, 0 CAR = 0.005 % (at $p < .05$). Technological Alliances CAR = 0.011(at $p < .001$); Marketing = 0.002 (insignificant).	CAR across all Joint Ventures = 0.87% (at $p < .01$). Related JVs CAR = 1.32 % (at $p < .01$). Technology exchange JVs CAR = 0.80 and Marketing JVs CAR = 0.01%, but significance varies according to test applied.	AR on Day 0 assessed by the information load faced by investors in each of 3 industrial clusters. Light load AR = 0.287; medium = 0.042; heavy = 0.119. All results statistically significant.	CAR for all JV = 0.73% at $p < .01$. CARs are relatively consistent and significant across all industries.	CAR for all JV = -0.3% which is insignificant for Z and % positive negative tests. Positive CARs are related to existence of insider ownership and level of leverage.	(FTSE Adjusted Models) Abnormal Returns on day 0 for all alliances = 7.5% Prestige Alliance AR = 9.702%. Regional Alliance ARs = 5.44%. All results significant at $p < .01$

Paper	Chan et al, 1997	Das, Sen and Sengupta, 1998	Koh and Venkatraman, 1991	Madhavan and Prescott, 1995	McConnell and Nantell, 1985	Reuter and Miller 1997	Mc Namara 1999
Size effects observed	Size of firm is inversely related to the magnitude of the event effect.	Negative relationship between firm size and profitability of SA. Smallest firms achieve greatest AR.	Small firms experience CAR 1.13%; large firms CAR 0.63%, both statistically significant.	AR for small and large firms is not statistically different.	CAR for small firms 1.10%; large firms 0.63%. Both results are statistically significant.	Size of firm has a moderate and significant effect upon CAR.	N/A
Period of study	1983-1992	1987-1991	1972-1986	1978-1991	1972-1979	Qtr. 1 1988-Qtr. 4 1994	Dec 1995 – Jan 1999
Estimation Window	-170 to 21 days	-200 to 10 days	-200 to 71 days	-60 to -15 days	-180 to -61 days	-250 to -50	-180 to -20
Event Windows studied	-20, +5; -20, -11; -10, -1; 1, 5; -1; 0; +1.	-3, +3; -2, +2; -1, +1; -1, 0; 0, -1; -1, +2; -1, +3; -3, +1; -2, +1.	-1, 0.	-5, -1; -5, +5; -2, +2; -2, -1; -2, 0; -1, +1; -1, 0; 0, +1.	-1, 0.	-2, +2; -1, +1;	-5, +5; -4, +4; -3, +3; -2, +2; -1, +1; 0.
> 1 model used to assess ARs?	No	No	No	No	No	No	Yes. 6 models employed. 3 CAPM and 3 adjusted returns models.
Industrial focus	More than 20 industries.	Informational Technology firms only.	11 industries.	6 industries.	More than 7 industries.	Not stated.	Biotechnology firms only.
Source of prices/ origin of listing	Centre for Research in Security Prices. Firms listed on US stock exchanges.	Centre for Research in Security Prices. Firms listed on US stock exchanges.	Centre for Research in Security Prices. Firms listed on US stock exchanges.	Centre for Research in Security Prices. Firms listed on US stock exchanges.	Centre for Research in Security Prices. Firms listed on US stock exchanges.	Centre for Research in Security Prices. Firms listed on US stock exchanges.	Datastream International. Firms quotes on UK exchanges.
Source of event announcements	Lexis/Nexis database search of business newswire services.	Wall Street Journal and Financial Times.	Wall Street Journal.	Wall Street Journal and Mergers & Acquisitions.	Wall Street Journal.	Predicasts Funk and Scott Index; Wall Street Journal	Company Websites; Financial Times; Reuters Business Briefing

TABLE FOURTEEN: A HIERARCHY OF WEALTH CREATION

Announcement of:	Average Abnormal Returns on Day Zero	Lowest Level of Significance Reported	Exploration Information	Exploitation Information
Prestige Alliance	10.04%	1%	Uncertainty reduction in Discovery projects that are part of the alliance. Cost sharing and access to complementary technology. Opportunities to learn development capabilities from the world leaders.	Milestone payments (appropriation), Uncertainty reduction in Development, cost sharing, access to top quality development and marketing capabilities.
Phase II/III clinical trials	9.32%	1% (parametric) 5% (rank test)	None	Uncertainty reduction in Development process.
Regional Alliances	5.41%	1%	Cost sharing and access to complementary technology. Learning opportunities may exist but would be lower than from a Prestige partner.	Cost sharing, access to top quality development and marketing capabilities.
Discovery/Phase I clinical trials	2.77%	5% (parametric) 10% (rank test)	Uncertainty reduction in the Exploration process.	None

FIGURE ONE: DAILY ABNORMAL RETURNS FOR ALL EVENTS (mean adjusted returns model)

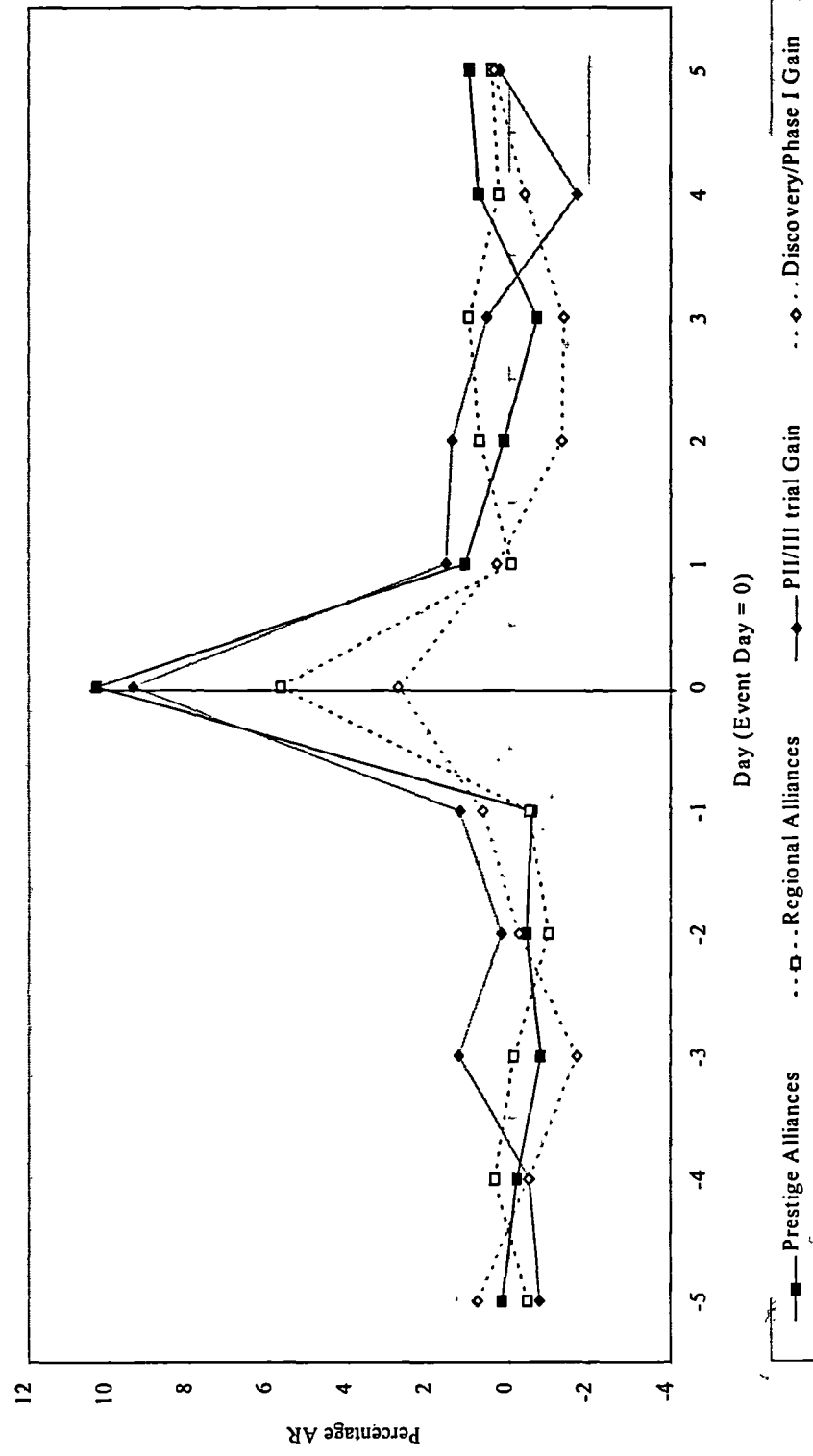
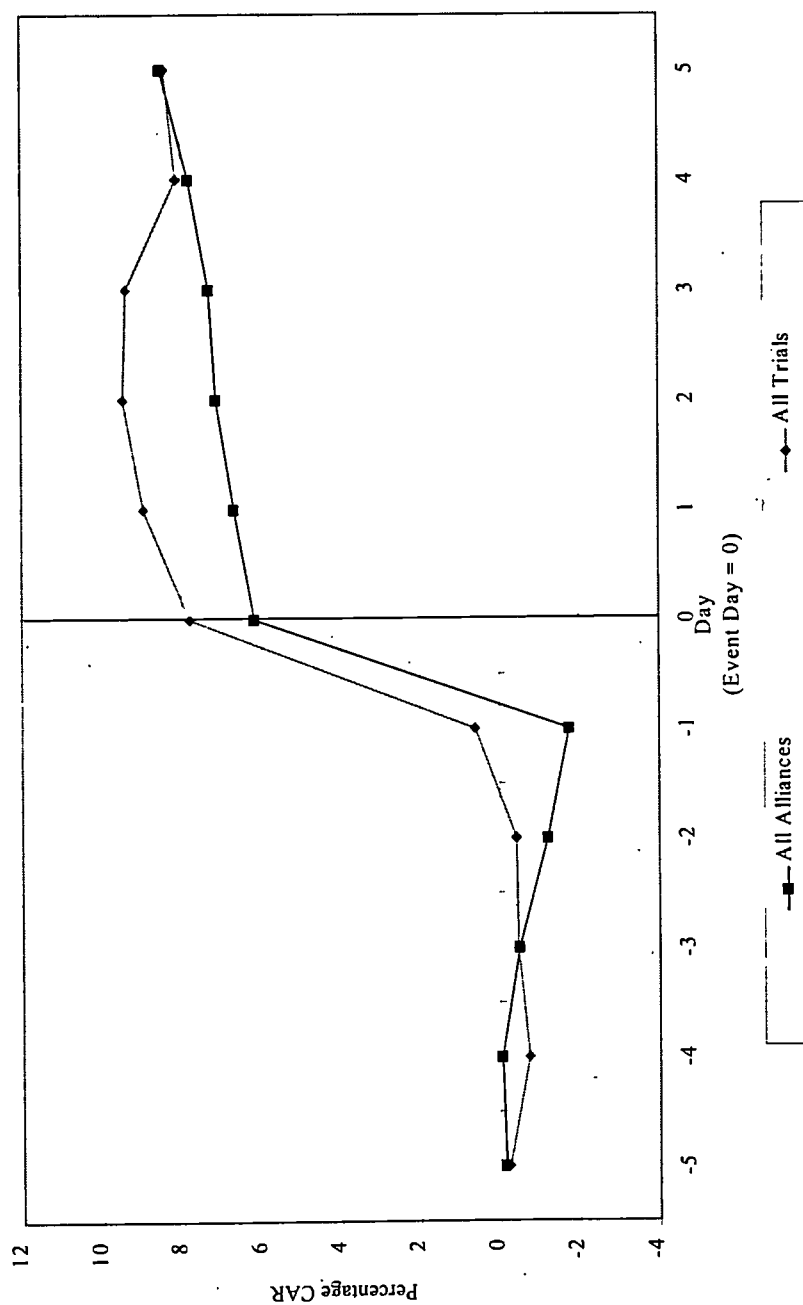


FIGURE TWO: CUMULATIVE ABNORMAL RETURNS FOR ALL ALLIANCES AND ALL TRIALS (mean adjusted returns model)



Chapter five

Conclusions

This thesis studied the tension between Exploration for new organisational knowledge and Exploitation of current stocks knowledge. This tension has received considerable attention in the literature (Cohen and Levinthal, 1990; Kogut and Zander, 1992; Levinthal, 1997; and Levinthal and March, 1993), but much of this has tended to be conceptual in nature and thus there remains much scope for empirical studies on this topic. Prior literature has argued that over time investment in Exploitation tends to occur at the expense of Exploration investments. It is argued that this occurs due to the more casually unambiguous and shorter feedback loops between investments in Exploitation activities and financial performance. On the other hand it is argued that feedback loops between Exploration activities and financial performance are both causally ambiguous and temporally distant (Levinthal and March, 1993). The arguments underpinning this literature were reviewed in Chapter Two and the major findings of that chapter are discussed below.

Having explored the conceptual tension between Exploration and Exploitation and offered insights into how this tension could be managed these ideas were explored within the context of an in-depth case study on Celltech, one of the oldest biotechnology firms in Britain. There is little prior literature that empirically examines a case firm in the context of the tension between Exploration and Exploitation. As such this case offers fresh insights into the management of this tension inside a real firm. The findings of this case and its implications for the literature are discussed in the following section of this chapter. A key output of the Celltech study was that Exploration activities may have relatively direct and powerful feedback loops with financial performance on the stock market. This observation appears to challenge an important convention in the literature and was thus explored in more depth via an event study in Chapter Four. The findings of Chapter Three and Four combined indicate that Exploration activities are financially valuable, that this value can be

observed, and that the tension between Exploration and Exploitation can be managed and balanced inside a real organisation. The findings of both Chapters Three and Four are also discussed in the following section.

Following a discussion of the findings of the Chapters Two, Three and Four, which are linked to the three main research questions outlined in Chapter One, three limitations of this research are highlighted and discussed. These limitations are: small sample size, caused by the youth of the sector; single sector bias; and sector specific operationalisation of variables. In closing this chapter three more general conclusions that emerge from the findings of this research are highlighted and discussed. These conclusions also summarised in Table Two of this chapter.

The first conclusion is that there now exists some empirical data, albeit limited by sector and sample size, that indicates that both Exploration and Exploitation activities can in fact be measured and feedback from financial markets observed. The measures provided in this research offer some guidance for future researchers who may wish to study Exploration and Exploitation effects in other sectors. The second conclusion is that observation of stock market reactions to the outputs of Exploration and Development activities may be of assistance to operational managers in both large and small firms when seeking to value the potential financial contribution of such projects. Such valuation may be of aid in assessing which projects in their portfolio should continue and which are in need of serious re-evaluation. Such valuations may also be of help in the creation of systems to reward key staff engaged in Exploration and Development activities. The third general conclusion is that *formation of alliances to conduct Exploration and Development projects can aid value creation*. In forming alliances small firms need to be mindful not only of the value that a partner can create by the resources and capabilities it invests in the project but also reputational effects. Formation of an alliance with prestige partners, who have a strong scientific and commercial reputation within the stock market, can have a considerable effect on the small firm's share price. This is because creation of such an alliance may contain additional uncertainty reduction information that is of value to the small firm's shareholders.

THE MAIN FINDINGS OF THIS THESIS: RESEARCH QUESTIONS RE-VISITED

Relating the findings of Chapter Two to the research question one

At the beginning of Chapter One the first research question that this thesis sought to address was stated as follows:

1. *From a theoretical perspective, what is the knowledge Exploration/Exploitation dilemma?*

This question consists of two sub questions:

- (a) From a theoretical perspective why should there be a tension between knowledge Exploration and Exploitation?
- (b) From a theoretical perspective why is it difficult to sustain efforts to increase knowledge stocks through Exploration or to appropriate a return from current knowledge stocks through Exploitation?

These questions were explored in Chapter Two. The chapter sought to undertake a literature review and interpret it in the context of the Exploration/Exploitation Debate. The tension between Exploration and Exploitation was argued to be due to the conflicting goals of each process. Exploration was defined in Chapter Two “as activities that seek to create new stocks of organisational knowledge through the search for and assimilation of new knowledge originating from the external environment, or through internal research activities.” Exploration seeks to widen the firm’s stocks of new knowledge. These new stocks expand the breath of strategic options open to the firm. Exploration offers the firm a window into new technologies and managerial systems that may become the core competencies, or products, of the firm in the future. At its heart Exploration is the attempt to maximise the gains from diversity of technology and processes. Exploration is about increasing the strategic and operational flexibility of the firm: creating new opportunities, encouraging new ways

of thinking about how the firm can be managed, envisioning and exploring new technologies and processes. Exploitation, on the other hand, was argued to be about incremental extension of current stocks of organisational knowledge and activities that appropriate a return from current stocks. At the heart of Exploitation is the attempt to maximise the benefits of specialisation.

Thus there is an immediate tension between Exploration and Exploitation. Exploration seeks to target the firm's resources at the creation of new stocks of knowledge. Exploration investments in their extreme pursue a belief that the value adding engine of a company is the creation of new stocks of organisational knowledge, whereas Exploitation seeks to target the firm's resources at appropriation of a return from current stocks of knowledge and the incremental improvement of such stocks. It was argued in Chapter Two that the tension between these processes needs to be carefully managed as if one dominates over the other for a sustained period of time the survival of the firm may be jeopardised. If the firm over invests in Exploration activities for a sustained period of time then it runs the risk sub-optimal returns for investors, and also exhausting its capital base. This is because it begins to fail to sufficiently exploit its innovations and thus has insufficient revenues generated by sales of products or services in the marketplace to provide a satisfactory return on investment to shareholders. If the firm over invests in Exploitation activities then a point will come when incremental improvements in its current stocks of knowledge will not yield efficiency improvements as great as those achieved by competitors with next generation technologies and processes. Nor will the firm's portfolio of products match the evolving needs of customers, thus the firm will experience reduced profits and eventually either withdraw from the marketplace or be driven out by fitter competitors.

It was argued in Chapter Two that Development mediates the relationship between Exploration for new stocks of knowledge and Appropriation of a return from current stocks of knowledge. Development was defined in Chapter Two as "activities that seek to expand, or reconfigure, the current boundaries of stocks of organisational knowledge through a process of deepening understanding of the current stocks of organisational knowledge by learning associated with the decent of experience curves.

The goal of Development is the expansion of a firm's stock of knowledge into formats that facilitate Use for Appropriation." The relationship between both Exploration and Exploitation (Development and Use for Appropriation) was described as largely complementary in the long term. The process of Development relies on the process of Exploration to provide a new stream of knowledge that can be incrementally expanded. Without this the firm would eventually run out of incremental development opportunities. The new knowledge generated by Exploration also acts as a reference point for products and routines being incrementally developed. Comparison of Exploration and Development activities raises the question as to whether incremental development of current products and services will yield greater efficiency improvements and attract more customers than ideas emerging from the process of Exploration. If not the question becomes should the current knowledge be phased out and the new installed. If so the practicalities of converting new stocks of knowledge created by the process of Exploration into products and services, or new more efficient and effective routines, requires Development. New technologies and processes do not emerge from Exploration fully formed. They require adaptation to fit into the current workings of the organisation. Thus it was argued in Chapter Two that there is a clear link between Exploration, Development and Use for Appropriation.

Reasons were offered in Chapter Two as to why it is difficult maintain a balance across Exploration, Development and Use for Appropriation and also why it is difficult to sustain efforts in each individual process over time. It was argued that three accompanying antagonists impede these processes.

Core rigidities can impede the process of Exploration. As noted in Chapter Two, core rigidities are sets of knowledge, which although valuable now, are inappropriate to future needs of the organisation. Outward looking absorptive capacities³⁸ play an important role in the process of Exploration but core rigidities can dilute, or in extreme cases extinguish, a firm's outward looking absorptive capacities and efforts by the firm

³⁸ One may recall from Chapter Two that outward looking absorptive capacities incorporate the ability to recognise and assimilate external knowledge into the firm.

to internally create new knowledge through recombination. Core rigidities encourage the firm to focus upon an ever-narrowing set of capabilities, as a result of sustained specialisation. The predisposition of the firm becomes to solve both the challenges and opportunities offered by the market through use of current technologies and capabilities rather than exploration for new, and potentially more efficient and effective capabilities and technologies.

Chapter Two argues that a slow rate of learning can impede the process of Development. It notes that the benefits of riding down a firm's learning curve are not automatic, but a result of deliberate action to improve costs and sustain yields (Hatch and Mowery, 1998). It was argued that a slow rate of learning impedes a firm's ability to incrementally improve the firm's current stock of knowledge by failing to continuously take proactive action to descend its learning curves. The argument is that over time, as a firm incrementally improves its capabilities and technologies, it may become complacent, believing that incremental improvements have made its capabilities as efficient and effective as practical. Thus the firm begins to become progressively slower in taking proactive action to search out incremental improvements, though such improvements may in fact exist. This results in sub-optimal descent of learning curves, and hence impedes Development. Competitors who are more proactive in pursuit of incremental improvements may eventually overtake such firms in learning races, even where their initial stock of knowledge was smaller.

Chapter Two argues that imitation by competitors poses a challenge to sustained appropriation of a return from current stocks of organisational knowledge. It was argued that imitation by competitors is essentially a process of the imitator's outward looking absorptive capacities competing with the innovator's inward looking absorptive capacities³⁹. The imitator seeks to capture a share of the innovator's profits through erosion of its competitive advantage, while the innovator seeks to maximise

³⁹ One may recall from Chapter Two that inward looking absorptive capacities facilitate speedy transfer of knowledge across intra-organisational boundaries. These help the firm to rapidly transfer knowledge of cost saving technologies and routines across the firm or transfer of new product and service concepts across the firm as quickly as possible to facilitate market penetration.

the profits from its innovation by speedy appropriation in the market as facilitated by efficient and effective inward bound absorptive capacities. Such imitation by competitors places pressure on the firm's inward absorptive capacities to become ever quicker at the dissemination of knowledge generated in one sub-unit of the firm to other relevant sub-units and its assimilation by those sub-units, thus enabling wider appropriation of a return from that organisational knowledge.

It was argued that the goals of the processes of Exploration, Development and Use for Appropriation, while complementary in the long term, could be antagonistic to each other in the shorter term. Equally it was argued that Core Rigidities, Slow Rates of Learning, and Imitation by competitors can reinforce each other. The implication of these arguments is that Exploration, Development and Use for Appropriation should not be managed as independent portfolios, but rather as an inter-connected system. This is because in the long term they are complimentary to each other and essential to the survival of the firm and also because difficulties in one area may impact strongly upon the other. Should a portfolio approach be employed then the impact of problems in one process upon another may not be recognised. Inaction in one area may reinforce problems in another. For example inaction in Exploration may eventually mean that the firm runs out of Development opportunities. As noted in Chapter Two delays in recognition of such inter-relationships could be potentially costly with, for example, the onset of a core rigidity reinforcing a Slow Rate of Learning and thus impeding progress not only in Exploration but also in Development.

The relationships between the processes of Exploration, Development, and Use for Appropriation on the one hand and Core Rigidities, Slow Rate of Learning and Imitation on the other were argued to be intermediated by three general characteristics of the firm, namely Intellectual Diversity, Social Interaction and Codification of knowledge. It was argued that changes in these characteristics could trigger movements between processes, for example changes in Intellectual Diversity could stimulate Exploration and repress Core Rigidities. The discussion of these issues in Chapter Two moved the literature forward by acting as a literature review and synthesis combining diverse strands of the literature to develop an improved

understanding of the balance between Exploration and Exploitation. The overall discussion was summarised pictorially in Figure Five of Chapter Two.

Arising from the above arguments about interconnectivity four propositions linking Exploration/Exploitation to generation of shareholder value were derived. These propositions were as follows:

Proposition One: Exploitation is more fully characterised as two related, but distinct processes: Development and Use for Appropriation. It is possible for both concepts to be separately identified and measured in real organisational contexts. It is then possible for each factor to be assigned a value by the market.

Proposition two: Both Exploration and Exploitation activities generate financial value for the firm. It is possible for this financial value added to be estimated from individual announcements of the outputs of Exploration, Development and Use for Appropriation activities in an independent firm with relatively few projects.

Proposition Three: The value generated by a firm will be greater when the processes of Exploration, Development and Use for Appropriation are managed as an inter-dependent set of activities than when managed as a portfolio of three separate activities.

Proposition Four: Where balance between Exploration and Exploitation is maintained over the long term then value added is greater than when the dilemma is managed by a series of periods, where Exploration dominates in one and Exploitation in the other.

Propositions one and two were empirically explored in this thesis. Propositions three and four while theoretically derived in this thesis were not empirically explored and thus open to future empirical testing.

Relating the findings of Chapter Three to research question two

It was found in Chapter Three that it was possible to operationalise Exploration, Development and Use for Appropriation into measurable terms inside a real firm. This has important implications for the Exploration/Exploitation debate because it enables empirical exploration of an important theoretical issue. Each process was measured in terms of inputs and outputs. Input measures focused upon the numbers of employees dedicated to Exploration or Exploitation activities inside a case firm, Celltech. Output measures focused upon the financial revenues that Exploration versus Exploitation projects raised, but also separated the R&D and commercialisation process of drugs into Exploration/Exploitation terms. Discovery research and Phase I clinical trials were classified as exploration. Phase II and III trials were classified as Development, while alliance formation was classified as predominantly appropriation. Creation of input and output measures, though crude, enabled exploration of the second research question of this thesis. The second research question was stated in Chapter one as follows:

2. *Is there evidence within a real organisational context that a firm's activities can be explained through the conceptual lens of balancing a tension between knowledge Exploration and Exploitation?*

This question consists of three sub questions:

- (a) Can a firm's activities over time be categorised in terms of knowledge Exploration and Exploitation?
- (b) Does this analysis indicate that Exploration and Exploitation activities are in balance or not?
- (c) If a tension between balancing Exploration and Exploitation activities is found to exist then how does a firm's executive team manage this tension?

By exploring part (a) of this research question, the first proposition of Chapter Two is addressed. Development and Use for Appropriation are separately identified and measured in the context of the Celltech case study. Operationalisation of these concepts is not a simple matter and as such the work on Celltech moves this literature forward in the arena of a high technology sector. Operationalisation of these concepts

enables part (b) of research question two to be addressed. Based on input and output measures it was argued that prior to 1990 Exploitation (Development and Use for Appropriation) was favoured over Exploration investments in Celltech. The financial and organisational renewal of Celltech was shown to coincide with a re-emphasis of the role of Exploration inside the firm, as measured by an increase in the inputs devoted to Exploration, coupled with the emergence of revenues generated by Exploration activities. It was found that in terms of inputs and outputs Exploitation dominated Celltech between 1985 to 1990, while balance between Exploration and Exploitation was maintained between 1992 to 1996 (see Figure One, Chapter Two for input measures and Figures Three and Four, Chapter Two, for output measures).

Part (c) of research question two was addressed in Chapter Three and the accompanying case study in Appendix One on Celltech. It was shown that some of the characteristics of the firm suggested in Chapter Two could stimulate movement between Exploration, Development and Use for Appropriation and their accompanying antagonists. Unlearning and injection of Intellectual Diversity into the firm via personnel turnover and re-organisation of teams was shown to diminish the effects of core rigidities and promote the re-emergence of Exploration. Dynamic management of organisational slack and creation of a shared language was shown to positively effect experimentation and hence promote Development activities. Other more traditional managerial methods were also shown to play an important role in the promotion of Exploration. These included the existence of an external threat to the survival of the firm, in the case of Celltech the bankruptcy of the major shareholder coupled with declining margins (see Figure Two, Chapter Three), and creation of an alliance network to gain access to key development and commercialisation resources and capabilities that the firm lacked. Such resources and capabilities were central to the firm's reassertion of Exploration and creation of a pipeline of innovative drug compounds.

Insights into the management of the tension between Exploration and Exploitation were offered from the experiences of Celltech. It was observed that innovation in appropriation coupled with installation of basic management review systems played an

important role in the management of this tension. Innovation in the financing of Exploration was particularly important in the process. By creating a network of prestige alliance partners Celltech was able to increase access to funds for Exploration activities from two sources: partners and the stock market. Partners provided financial payments upon achievement of milestones in the R&D process. Shareholders used such alliances as a signal of the value of Exploration projects within the firm, rewarding the firm with increased share price, thus making future equity offerings easier for management to undertake.

The most powerful example of the interaction between stock market funds and alliance partner relationships was in the case of the Celltech-Bayer alliance. As argued in Chapter Three (and supported by Appendix One) when Bayer was willing to invest a potential £ 26 million in milestone payments (of which £ 15.6 million were actually paid during the life of the Celltech-Bayer alliance), and dedicate both significant development capabilities and managerial resources to an alliance on the CDP 571 septic shock drug project with Celltech, investors used this as a validation of Celltech's technology and the future value of its Exploration activities. Celltech was able to use this validity effect to launch an IPO in 1993. This IPO raised over £ 30 million new equity funds, much of which was used to fund future Exploration projects. This innovation in financing of Exploration made such investments more viable to Celltech and thus diminished the short-term pressure towards generation of funds through Exploitation activities.

Having diminished the pull of over Exploitation it was important for the firm to put in place internal mechanisms to ensure that the large funds generated by the IPO did not stimulate over investment in Exploration to the exclusion of Exploitation. Thus management put in place a series of managerial review systems that sought to explicitly link research to development and thence to the marketplace. These review systems were detailed in Chapter Three and Appendix One.

These findings have three interesting implications. First, the operationalisation of Exploration and Exploitation in the context of Celltech shows that this theory can be

applied within real firms with real challenges, such as renewal. It can be seen that changes in the balance between Exploration and Exploitation can have a real effect on the success of such a firm. In the case of Celltech movement away from Exploitation and towards Exploration stimulated a very powerful renewal of the firms fortunes. Secondly, it can be seen that despite the tensions between Exploration and Exploitation, as theoretically outlined in Chapter Two, it is possible within a real organisation to maintain a balance between the two activities in terms of inputs and outputs over a sustained period of time (1992-1996). Third, Chapter Three provided an insight into how Exploration and Exploitation are managed in a real organisational setting. Lessons may be learnt from the experience of UK biotechnology companies in innovation in the finance of Exploration that could be applied in other sectors to stimulate their own Exploration or renewal efforts.

Relating the findings of Chapter Four to research question three

In Chapter One the third research question that this thesis sought to address was stated as follows:

3. *Do the financial markets reward announcements of Exploitation activities with higher returns than Exploration activities, as predicted by theory?*

Drawing upon the literature review this general research question was elaborated upon in more detail via propositions two to four in Chapter Two. These were further refined into a series of six hypotheses on the relationship between Exploration/Exploitation and shareholder value in Chapter Four. These hypothesis were based both upon knowledge gained from a further review of literature and the experiences of in-depth case study companies. It was found that in keeping with the thrust of proposition two announcements about Exploration, Development and Use for Appropriation could be identified in the financial press and corporate web-sites. Using this information the impact of such announcements upon shareholder value could be assessed using the event study methodology. It was found that positive announcements about Exploration, Development and Use for Appropriation (as operationalised in Chapters Three and

Four) did coincide with rises in the share price of the firm over and above the performance of both market indices and historical performance of the firm's own share price. This general finding offers important support to the observation in Chapter Three that investments in Exploration can generate real shareholder wealth in addition to being a potential source of funds through milestone payments and equity raised via an IPO or follow-on offerings. Propositions three and four were not empirically analysed using the event study in Chapter Four and remain theoretical observations rather than empirical facts.

Four types of event were analysed in Chapter Four. Prestige alliances were identified as being particularly valuable due to the information they provide shareholders on Exploitation activities (Development and Use for Appropriation), in addition to offering signals on the value of Exploration projects. PII/PIII clinical trials were argued to offer shareholders rich information on Development. Regional Alliances were argued to offer information on Development, while Discovery and PI announcements were classified as Exploration activities.

A summary of the findings of the event study is provided in Table One of this chapter. This table offers a brief summary of the hypothesis, for a full reproduction the reader is referred to Chapter Four. This table offers information on the number and type of events studied for each hypothesis, the abnormal returns generated by two models, namely, UK Bio⁴⁰ and the Average Adjusted Returns⁴¹ model. These two models were chosen as representative of the results generated by all six models and because of their

⁴⁰ The reader will recall from Chapter Four that the UK bio model tests the significance of the change in a share price in response to a given event over a specified event window against the performance of an index of UK biotechnology stocks (weighted by market capitalisation) over the same event window. In the case of Table One, Chapter Five the event period is the event day zero. In the case of Chapter Four various event windows were analysed. The narrowest event window was day zero, the widest was day – 5 to day +5.

⁴¹ The reader will recall from Chapter Four that the Average Returns model tests the significance of the change in a share price in response to a given event over a specified event against the average performance of that share during the estimation period from day –180 to day -20.

industry specific nature. Models employing the FTSE All Share index as a benchmark for calculation of abnormal returns generated similar results to both the UK Bio and Average Returns models. The significance of the returns generated by these models is provided using both a parametric test and, due to small sample size, a simple percentage positive/negative non-parametric test result is also provided. From Table One (of Chapter Five) it can be seen that hypothesis one, two, three and five are all strongly supported by the analysis, while hypothesis four and six obtain a medium level of support. In Chapter Four, Table One, it was observed that the majority of the effect of a given announcement in this sample occurred on day zero⁴², thus in Table One of Chapter Five, all reported Abnormal Returns are for a single day event window, namely the event day zero.

INSERT TABLE ONE ABOUT HERE

Alliances were identified in both the in-depth case studies and the literature review in Chapter Four as playing an important role in value creation. Hypothesis one sought to determine if the announcement of a new alliance between the sample biotechnology firms and pharmaceutical or other biotechnology partners would add shareholder value. This tested a belief by managers within the case firms that alliances played a crucial role in both the creation of new stocks of knowledge and incremental development of current stocks and thence the creation of shareholder value. Alliances were argued to bring with them resources and capabilities that the case biotechnology firm's needed to take their promising drug candidates through the regulatory development process and on to the market. It was also argued that alliances played a role in validating the value of scientific work undertaken inside the firm in the eyes of shareholders. Alliances also enabled firm's to obtain cash payments based on work still in Exploration or Development stages, thus enabling firm's to better balance the pressures for innovative Exploration against the need for short-term financial gains that Exploitation through sales in end markets bring.

⁴² From Table One, Chapter Four, it can be observed that the largest abnormal returns were on average experienced on day zero and that with the exclusion of Discovery/PI events these returns were significant at the 1% level using both parametric and non-parametric tests. Discovery and PI events were significant at the 5% level.

The results of the event study clearly indicated that announcements about the formation of alliances had a strong impact on share price generating abnormal returns of 7.5% (UK Bio model) and 7.9% (Average Adjusted Returns model), both of which were significant at the 1% level. This is an important finding insofar as it supports both the assertions of case study interviewees and observations from the literature.

Hypothesis two sought to test if the type of alliance partner resulted in greater abnormal returns. A belief was expressed by interviewees that alliances with prestige partners, operationalised as any firm in the top 20 in terms of global pharmaceutical sales, had a very strong effect on shareholder value. This they argued was because these firms brought world class development and marketing capabilities, which made the passage of a drug through the regulatory process more efficient and effective, and also increased market penetration if approved by regulators, due to access to distribution and marketing channels. The reputation literature would suggest that these alliances should be very valuable due to the positive signalling effects that they offer shareholders as to the potential of a project in which they participate.

Interviewees argued that these effects would be larger for prestige alliances than all others. The data confirmed their intuition. Prestige Alliances generate nearly twice as much abnormal returns as Regional Alliances, 10.1 % versus 5.1% using the UK Bio model and 10.0% versus 5.4% using the Average Returns model. All results were significant at the 1% level. Confirmation of this hypothesis made an important contribution because it once more confirmed the intuition of case managers and also because it added a weight of evidence to the argument in the literature that partner reputation is an important factor in determination of alliance effect upon shareholder value.

Hypothesis three sought to establish if announcements of progress in clinical trials resulted in abnormal returns. It was the view of the case companies that this should occur. Similarly an argument can be made based on the literature that such announcements should add value as they provide important uncertainty reduction

information to shareholders. Again the intuition of case managers was supported by the data. Announcements of progress in R&D generated abnormal returns of 6.6% (UK Bio model) and 7.2% (Average Returns model), both of which were significant at the 1% level.

Hypothesis four sought to establish if news about later trials attracted greater abnormal returns than earlier ones. It was argued that this should be the case from an Exploration/Exploitation perspective. According to the predictions of Levinthal and March (1993) Exploitation announcements should generate greater returns than Exploration announcements. Discovery/PI clinical trials were classified as Exploration announcements, while Phase II/III clinical trials were classified as Development (Exploitation) announcements. Once again the hypothesis was supported, though in this case the power of this support was lower. PII/III announcements were associated with abnormal returns over three times greater than those of Discovery/PI announcements, 8.6% versus 2.7% (UK bio model) and 9.4% versus 2.8% (Average Returns model). Abnormal returns for PII/III announcements were significant at the 1% level, with the exception of the non-parametric test for the Average Returns model, which was significant at the 2.5% level. Abnormal returns for Discovery/PI announcements were significant at the 5% level, with the exception of the non-parametric test for the Average Returns model, which was significant at the 10% level. The lower significance levels mean that hypothesis four only gained medium support. The implications of this finding are none the less important. Events were classified as Exploration or Development (Exploitation) announcements and *both* generated positive abnormal returns, thus both are associated with shareholder value. Table Twelve of Chapter Four indicates that while the sample of Exploration announcements may have been too small to confidently state that a statistical relationship between announcements of Exploration events and shareholder wealth increases exists one can observe that at an individual level such announcements are important. Three announcements in that table generated very large abnormal returns of £ 30.5 million, £ 15 million and £ 6.1 million respectively.

Hypothesis five sought to test if announcements of alliances and R&D progress were roughly the same. The case companies argued that *both* alliances and progress in R&D played a vital role in their success. They argued that medium term survival required both a growing portfolio of drug candidates in various stages of development and a growing portfolio of alliance partners. Analysis of the data suggests that on average an announcement of each of these two event categories generates approximately the same abnormal returns. Again this confirms the intuition of case managers through analysis of data from a larger sample of firms. Table One indicates that Alliances generated abnormal returns of 7.5% (UK Bio model) and 7.9% (Average Abnormal Returns model) versus 6.6% and 7.2% generated by announcements of R&D progress. These returns while not identical and very similar and support the belief that both alliances and progress in clinical trials are viewed as important value generating activities by shareholders.

Hypothesis six sought to test if a hierarchy of announcements existed that would mirror arguments about value creation and Exploration/Exploitation. It was argued that announcements that were richest in information about both Exploration and Exploitation should generate the greatest returns. Chapter Five argued that Prestige Alliances offered rich information to shareholders about the value of a biotechnology firm's Exploration projects, reduced the uncertainty attached to Development, and provided short and medium term financial rewards via milestone payments, thus they should be associated with the greatest abnormal returns. PII/III results should be next highest, because they offer rich information about uncertainty reduction and progress in the process of Development. Regional Alliances offer the next highest returns because they transmit uncertainty reduction information in Development, through access to scarce resources and capabilities, but do not provide as certain information as bestowed by positive results from PII/III clinical trials. Announcements of Discovery/PI trials are classified as Exploration and should bestow the lowest abnormal returns because of their distance from the market and financial returns, as predicted by Levinthal and March (1993). The results of Table One offer medium support to this hypothesis. Prestige Alliances do result in the largest abnormal returns, 10.1% (UK Bio model) and 10.0% (Average Returns model) however these are only

0.6% to 1.5% lower than returns associated with PII/III trials. Regional Alliances generate considerably lower abnormal returns of 5.1% (UK Bio model) and 5.4% (Average Returns model), with Discovery/PI trials generating abnormal returns of 2.7% and 2.8% respectively. These results do offer medium support for the hierarchy predicted in hypothesis six.

Reflections on the connections between the findings of Chapters Two, Three and Four

Overall Chapters Two to Four provide considerable theoretic and empirical insight into the relationship between Exploration and Exploitation. They cover a spectrum of methods from qualitative in-depth case studies through to quantitative analysis of the relationship between announcements and share price. Important linkages were observed between theory and practice, as highlighted in the Celltech case in Chapter Three. Importantly the intuitions and observations of managers inside case companies were often confirmed through empirical analysis of share price movements in Chapter Four. As predicted by managers in the case firms both progress in development of an alliance network, to access scarce resources and capabilities necessary to take a drug from conception through to commercialisation, and progress in the process of gaining regulatory approval were both found to trigger a positive response from shareholders. Though the intensity of this response varied from event to event, it was found that the average response of shareholders was in line with the financial predictions of the Exploration/Exploitation literature. Abnormal returns were largest in response to announcements rich in both Exploration and Exploitation information and smallest in response to Exploration information.

Qualitative evidence from the Celltech case, however, suggests that inside firms managers are not always driven towards Exploitation to the exclusion of Exploration, as the literature may suggest. In the case of Celltech a financial crisis resulted in a movement towards Exploration activities and away from Exploitation activities, rather than an immediate intensification of Exploitation activities. Chapter Four also offers insights that an event study could not provide, such as how is the tension between

Exploration and Exploitation managed inside firms themselves. The renewal of Celltech shows that financial value can be generated through Exploration activities long before they evolve into saleable products and services, or cost saving technologies and processes. It can be seen from Chapter Three that managing that tension requires not only an eye to the capital markets but also careful management controls to be installed. Much time was spent inside the firm ensuring that managerial systems were installed that sought to maintain a clear connection between Exploration for new compounds, Development, and Appropriation.

Qualitative and quantitative data collection and analysis have both played a role in this thesis. Individually each has offered insights into the management of organisational knowledge, combined they offer a richer insight into the management of the tension between Exploration and Exploitation and generate some interesting implications for both the literature and practice. Some of these have been touched upon already in this chapter, and individually in prior chapters. Having outlined some limitations of the study this thesis will close by highlighting three important implications of this study for both theory and practice.

LIMITATIONS OF THIS STUDY

Three limitations of this study can now identified and discussed. Efforts taken to minimise their effects are highlighted.

Small sample size

The number of observations analysed in Chapter Four was not large. Only 146 observations were available for the event study and due to methodological constraints only 55 could be analysed. It should be noted that the small number of events observed is a reflection of the relative youth of the sector. Data was only available for a sufficient number of firms from December 1995. Equally given the length of time available to complete this study data collection had to cease in January 1999. Within this period considerable effort was made to identify all relevant events. The reduction of the sample due to confounding events was taken in light of the advice of Mc

Williams et al. (1997). Their inclusion would have cast serious doubt on the reliability of the results of the event study.

By sub-dividing these 55 observations first into two groups and later four groups sample sizes became quite small. This means that the statistical power of the findings from these samples needs to be treated with some caution. To protect the validity of the study's findings both a parametric and non-parametric test was undertaken in line with the advice of Mac Kinlay (1997) and Mc Williams et al. (1997). It should be noted, however, that in Mac Kinlay's paper (1997) he shows that where abnormal returns are high (and variance across the sample low) then the ability of parametric test statistics to correctly reject the null hypothesis is very high even in the case of samples of 20 and fewer.

Mac Kinlay (1997) suggest that where statistical power is a concern the researcher should try to more accurately identify the event day, thus enabling a reduction in the length of the event window, and also employ a non-parametric sign test. It should be noted that in an effort to maximise the value-added of Chapter Four both of these suggestions were rigorously pursued. Much time was taken to carefully identify the event day enabling a reduction of the event window from 11 days, -5 to +5, to a very narrow window of day 0. Evidence from Table One, Chapter Four, suggests that this narrow event window captured the majority of the event effect and also increased the significance of the parametric test. Mac Kinlay (1997) observes that "inclusion of the non parametric tests provides a check of the robustness of conclusions based on parametric tests." In Chapter Four care was taken to only support a hypothesis were both the parametric and non-parametric tests had a high level of significance.

A second concern regarding the event study is that only eight usable Exploration events were observed over the period of the study. One measure taken to offset the statistical limitations that a sample of eight imposed was to report the absolute effects of each individual Exploration event in Table Twelve of Chapter Four. From this table it was seen that the variation in effect was very large. Some events had a very small impact on firms' market capitalisation, while three had a very large effect. Thus the

economic impact of individual Exploration events upon firms' market value was seen to be considerable.

A third concern was that while there was a clear, if small, sample of pure Exploration events, and a larger sample of Development events there was no pure sample of Use for Appropriation events. The impact of appropriation was combined with other effects in the announcement of Prestige Alliances, thus the individual impact of appropriation announcements was not identified. This problem is again largely a factor of the youth of the sector. As the sample of firms matures then more will announce the launch of a drug into the actual marketplace and announcements of sales levels will begin to emerge. Such announcements could then be analysed using the event study method, assuming of course that confounding events are not also present. In the future if a sufficient number of such events occur analysis by event study would be a potentially valuable research avenue, as it would enable more complete testing of the Exploration/Exploitation theory.

The results of Chapter Three impose another limitation upon the findings of this thesis. Embodied within the Celltech story is much of the experiences that the wider sector has faced. It is the oldest firm in the sector and has faced many of the major challenges that other UK biotechnology firms periodically experience: the tension between contract services and innovative R&D; replacement of the senior management team; success followed by disappointing results in both alliance formation and clinical trials; and seeking a listing on the London Stock Exchange. The case is thus illustrative of the challenges faced by managers in the sector and solutions applied to them. Nevertheless Celltech is a single case, therefore the insights offered in Chapter Three and the case study in the appendix are an illustrative, rather than definitive, statement of how Exploration/Exploitation is managed in the sector. Such a definitive statement might emerge if a follow-up study employing a large-scale questionnaire were undertaken.

Despite the small sample of case studies and events available to the researcher it should be noted that considerable effort was undertaken to maximise the power of the results obtained. Results of the qualitative case studies fed into the event study. The

event study was applied to a much larger sample than the case work and as such offered more statistically generalisable insights into the UK quoted biotechnology sector.

Sector bias

As was observed in Chapter One of this thesis the UK therapeutic biotechnology sector has several characteristics that make it unusual. First, it is a highly regulated sector. Before a firm can sell a drug over the counter or via a prescription to the general public it must undertake a number of clinical trials that prove to the regulatory authorities that the drug is both sufficiently safe and effective that it can be legally sold. To compensate for this high regulatory hurdle, which costs many millions of pounds to meet, firms are rewarded with monopoly rights through the patenting system.

Second, case interviewees, annual reports and news media sources often argue that returns are greatest from novel drug compounds. Creation of such compounds require considerable investment in R&D. Thus the sector is both subject to considerable regulation and is driven by R&D investments. Third, the technologies that the biotechnology sector is founded upon are relatively new. Private UK therapeutic biotechnology firms were not formed until the 1980s and the first did not seek a listing on the London Stock Exchange until the early 1990s. These three features, while not unique to the sector, are equally not common to all sectors of the UK economy. The reader therefore needs to consider industry specific conditions when seeking to generalise from this sample of biotechnology firms about the relationship between Exploration and Exploitation that one should expect in other sectors.

Operationalisation

Operationalisation of events in Chapter Four was by necessity quite sector specific. Classification of Exploration, Development and Use for Appropriation by stage of the R&D process and alliance formation should apply in the wider pharmaceutical sector, however direct application beyond this sector would not be practical. The study of Exploration and Exploitation in Chapter Three is more easily transferable across

sectors. Resource input measures should be applicable across sectors as should financial output measures. Specific non-financial output measures of Exploration and Development are, as in the case of this study, quite industry specific. To replicate this study in other sectors the researcher would need to identify key non-financial output measures of Exploration, and Development prior to undertaking the event study.

In summary the variables created in this thesis were by necessity quite industry specific. Their application offered insights into the operation of the tension between Exploration and Exploitation in the pharmaceuticals sector, which is a very important sector for the UK and the wider European and Global economies. Operationalisation of this theory in both Chapters Three and Four, despite their industry specific nature, also offers future researchers insights into the process by which such operationalisation can be undertaken.

IMPLICATIONS OF FINDINGS UPON THE LITERATURE AND MANAGEMENT POLICY

Much work has been undertaken in this thesis that advances the academic literature on the management of the tension between Exploration and Exploitation. These specific advances have been signalled both within individual chapters and specifically in prior sections of this concluding chapter. Chapter Two made an important contribution by reviewing and integrating past literature in addition to highlighting the interconnected nature of the tension between Exploration and Exploitation and the important intermediary role of Development. Chapters Three and Four undertook the important task of empirical exploration of the theory outlined in Chapter Two. Chapter Three made an important contribution by providing insights into how the tension between Exploration and Exploitation occurs inside a high technology firm. The contribution of Chapter Four was also important. It is the first empirical analysis, to this researcher's knowledge, of the response of financial markets to the outputs of the tension between Exploration and Exploitation, yet financial responses are cited in the literature as an explanation for why Exploitation comes to dominate over Exploration investments inside firms. The findings of this chapter confirmed the experiences of case managers. It also advanced the academic literature by actually testing in the field a theoretical

belief that Exploitation activities attract greater financial rewards in the short term than Exploration activities. It challenges the view that feedback loops between Exploration activities and financial reward are so complex that they may be unobserved, while confirming that in general the largest financial rewards are associated with announcements rich in Exploitation information. There is, however, evidence in Chapter Four that in some cases the markets react powerfully to announcements of progress in Exploration activities.

Each of these findings makes an important contribution to our knowledge of the tension between Exploration and Exploitation activities. Notwithstanding the limitations that were outlined above, it is argued that three more general and exciting conclusions can be drawn from the work embedded in this thesis. Firstly, Exploration activities can in certain circumstances attract strong and direct feedback from the stock market. Secondly, the announcements of small listed companies could act as an important benchmark for valuation of internal R&D projects inside large listed firms and the reward of key staff involved in such projects. Thirdly, that alliances may play an important reputational role in validation of risky R&D projects, adding value greater than from resource sharing and market access alone. These three implications are summarised in Table Two. This table repeats the three statements outlined above, links each statement to evidence in this thesis, and then outlines the key implications of such a statement. A more detailed discussion of each of the three implications is offered below.

INSERT TABLE TWO ABOUT HERE

Temporally distant Exploration activities can add observable shareholder value

The outputs of Exploration activities that are temporally very distant from final product markets, but that have a defined link to high value end markets, are valued by shareholders. In Chapter Four, Table Twelve, it can be seen that announcement of Phase I clinical trial results can add considerable value. The example of Chiroscience is quite illustrative. It announced that it had entered Phase I clinical trials for its MMP inhibitor and market capitalisation rose by £ 15 million. From Table One, Chapter

One, it can be seen that the average time to market from entry of Phase I clinical trials to market launch was almost nine years. Clearly this project was temporally distant from the final market place. The announcement was also clearly Exploration. The technology knowledge being Explored was novel from the perspective of both the firm and the external environment and its likely commercial application quite uncertain. From Table One, Chapter One, it can be seen that the probability of a drug that enters Phase I trials making it through to the final marketplace is 10%. Even then only 30% of the drugs that make it to the marketplace subsequently generate sufficient revenues to recoup the cost of R&D (Grabowski and Vernon, 1994).

In the specific case of the Chiroscience announcement, the medicinal application of MMP inhibitors, while a hot technology at the time, was still quite uncertain both from a technological and commercial perspective. It was known that MMPs played a role in a wide variety of diseases, however the exact role of compounds based upon MMP inhibitors in the treatment of such diseases was still quite uncertain. It was believed that MMP inhibitor technology was of considerable commercial potential, but only if it proved to have a medicinal application in high profile, profitable, illnesses. At the time it was believed that MMPs represented the opportunity to offer superior treatment in diseases, such as some cancers, where current treatments were not highly effective and the risk of death considerable. In this context the market saw Chiroscience's MMP inhibitor Exploration investment as quite distant from the final market, but of considerable long term financial value and thus rewarded the firm with a large and significant rise in market capitalisation.

One can envisage that this phenomenon can occur in many other industries. The challenge for management is to be innovative in how they finance such investments and signal their worth to shareholders. In the case of biotechnology firms the role of prestige alliances partners, as auditors of the value adding potential of the firm's Exploration investments, was very important. Formation of alliances with prestige partners may have considerable value adding potential in other sectors. Small non-biotechnology firms, who engage in high cost, temporally distant, and technologically complex Exploration projects may benefit from entry into alliance partnerships, where

such partners have a long past track record in delivery of both technologically sophisticated products to end consumers and high returns to investors. The issue of alliances is discussed in more detail in the closing section of this thesis.

Firms in other sectors may benefit from observation of shareholder reactions to progress in their own Exploration activities. To make such observations it would be necessary to obtain on-going signals from shareholders as to the future value of a given Exploration investment. This would require the firm to structure such investments so that that a series of outputs can be announced to the stock market and alliance partners indicating relative progress. In the case of biotechnology firms such milestones are easily identifiable as end points of one stage of clinical trials and the commencement of another. Clear identification of such milestones is facilitated by the need to prove to regulators that a drug has passed a series of rigorous clinical trials. In the absence of a regulatory requirement it may be possible for other sectors to construct a series of such nodal points, in co-operation with shareholders.

A key feature would be the provision of credible data to support assertions of success or failure at each node. Often results of pre-clinical and clinical trials are the subject of peer review in journal outlets. Such peer review articles, or the publication of the principal results and data from clinical trials enables outsiders, including shareholders, to judge the relative success of the Exploration project and hence its potential future value. If firms from other sectors could open their Exploration projects to such peer review then announcements of progress may be interpreted by shareholders and assigned a positive or negative response. This would shorten the feedback loop between Exploration investments and financial reward, thus enabling management to assess the value of on-going investments in Exploration more directly well before returns generated by final market sales could be observed.

The fact that Exploration activities are valued by the stock market has powerful implications for the literature on the balance between Exploration and Exploitation. Positive, validated, announcements about progress in Exploration and Development can have a strong positive effect on a firm's share price. Linkage of the outputs of

Exploration activities to stock market reactions may shorten the feedback loop between Exploration and financial reward. This may lessen the gravitational pull of investment in Exploitation activities to the exclusion of Exploration that is proposed in the literature, thus making the task of maintaining a balance between Exploration and Exploitation more viable for firms to achieve.

Small company listings could offer benchmarks for rewarding staff involved in Exploration and Development projects inside large firms

Where firms identify innovation as a key value driver for their business then management needs to put in place a system to acquire innovative products, services or processes. One extreme approach might be to outsource innovation, buying in innovative technologies and processes from the external environment, while maintaining sufficient outward bound absorptive capacities to internalise such externally created knowledge. Another approach might be to promote Exploration activities inside the firm itself. An important challenge is how to motivate and reward staff inside the firm to pursue Exploration investments that add shareholder value. One opportunity that may arise from this research project is to partially link the financial reward of key staff involved in Exploration projects to the shareholder value associated with the announcement of the outputs of such projects over time.

A conventional approach may be to offer share options that link in the employee to future shareholder value of the firm as a whole, thus the employee receives a financial reward based on the performance of the firm as a whole. Another approach might be to reward employees in response to direct rises in share price associated with announcements of the outputs of Exploration activities in which they played a central role. There is clear evidence in Chapter Four that positive announcements of progress in clinical trials have an identifiable effect on shareholder value. Such effects offer management an opportunity to value key Exploration and Development projects long before they generate products sold to end markets. These value effects could be used by small high technology firms to both reward staff who have played a key role in such projects and also assess the relative value adding impact of various projects undertaken

within the firm over time. Monitoring the response of shareholders to announcements of progress across a range of projects offers important learning opportunities to management. Over time they can observe which projects are consistently rejected by shareholders. Continued financial support of such projects in the face of unfavourable shareholder responses would require strong internal justifications of future value added, while funds made available by discontinuation could be channelled to projects that the owners of the firm believe to have greater potential value.

Announcements by small firms of progress in clinical trials have an identifiable effect on shareholder value in part because the firms are relatively small and hence the number of projects they announce relatively few. Larger firms, for example Glaxo-Wellcome, undertake a very large number of Exploration and Development projects simultaneously. Announcements from large firms are frequent, thus the likelihood of confounding events is considerable. The impact of announcement of a positive Phase II trial for example may be difficult to assess due to the high possibility that other events will be announced at a similar time. Such simultaneous announcements would act as confounding events and thus make an associated rise in shareholder value difficult to assign to the Phase II trial announcement alone. The average impact of a Phase II/III trial announcement in Chapter Four (Table Ten) was £ 12.2 million. In the case of the sample of UK biotechnology companies such announcements were associated with an average abnormal return across all six models of 9.3% for the firm as a whole. For individual projects at a large firm such as Glaxo-Wellcome a rise of £ 12.2 million in market capitalisation may represent a considerable success for the project team (assuming such a rise could be clearly identified). A series of such successful projects would have an important impact on the value of the firm as a whole, however their individual impact would be minimal. The overall impact of a £12.2 million movement in Glaxo-Wellcome's share price would be difficult to detect. The firm had a market capitalisation of approximately £ 60,150 million in January 2000. A £ 12.2 million movement would thus represent about 0.0002% of the firm's market capitalisation. Such a small percentage rise would be unlikely to generate a significant effect in an event study.

One way for such large firms to identify the value creating potential of projects may be to use the announcements of smaller firms as benchmarks or value creation proxies. In projects where the large firm is collaborating with a smaller biotechnology firm, listed on the stock market, it could monitor the movements in the share price of its biotechnology partner that are associated with announcements from the project. The pharmaceutical firm could then assess the proportion of that value attributable to its efforts and use this as a guide in the motivation and reward of its staff who are collaborating with the biotechnology firm on the given project.

For projects where the pharmaceutical firm is engaging in a wholly internal Exploration or Development project it could select similar projects in small biotechnology firms and use these as proxies. Announcements from projects with a similar technological and commercial profile could be monitored and their effect on the biotechnology firm's share price assessed. These effects could then be used, with caution, in assessing the value of a similar project inside the larger pharmaceutical firm. This valuation could be combined with internal accounting and scientific measures of the value of the project and then be used to determine financial rewards for key members of the project team. Benchmarking of this type can be most easily envisaged within the biotechnology and pharmaceutical sector. There are a large number of small listed companies working within the same regulatory framework as larger firms and because a large number of collaborative Exploration and Development projects are undertaken between large and small listed firms. It may well be possible for such value/performance benchmarks to be created in other sectors where a population of small and large quoted firms is present.

This form of benchmarking may enable such firms to inject external market responses into their valuation of internal Exploration projects. It could offer a mechanism by which the financial pull of Exploitation investments is reduced relative to that of Exploration. Key staff working on such temporarily distant projects could see the financial impact of their work and be rewarded for short term rises in market capitalisation long before the project produces products that are sold in the marketplace. This may be of help in both the motivation and reward of staff engaged in

key, but long-term, Exploration projects and also help management to maintain a balance between investment in, and reward of, Exploration versus Exploitation activities.

Alliance formation plays an important role in signalling the value of Exploration and Development activities

It can be seen from Chapters Three and Four that formation and on-going management of a network of alliance partners can play a strong role in the creation of value inside UK biotechnology firms. The role of alliances in value creation has been an important topic of research in the literature, as was highlighted in Chapter Four. The findings of this research are important in that they offer further evidence of the value adding effects of alliance formation and insights into what types of alliance add greatest value. It was found that alliances with prestige partners add greater value than with regional alliance partners. Importantly this research offered knowledge-based arguments as to why such alliances should create greater value. It is important to realise that value is not only created by access to superior development and marketing resources and capabilities, but also that reputational effects play an important role in the process of value creation.

Alliances with prestige partners add greater value in part because they offer shareholders insights into the quality of drug discovery and development activities inside biotechnology firms. Their endorsement of a particular project or firm adds value because they are believed to have powerful scientific and due diligence capabilities that greatly assist in the valuation of a drug discovery and development project. In entering into a partnership with a smaller firm the pharmaceutical firm will obtain access to scientific and commercial data on a project that, due to confidentiality concerns, is unlikely to be publicly available to shareholders. Major pharmaceutical firms have rich reserves of knowledge about the drug discovery and development process, which they can apply to assess the likely commercial success of a given project in which they are being invited to collaborate. Investment by the pharmaceutical firm offers important information to the shareholders of the

biotechnology firm. Entry into an alliance with the biotechnology firms suggests that its pharmaceutical partner believes the project has a favourable risk/return profile and will seek to improve that relationship by injecting its considerable expertise into the project. If the pharmaceutical partner has a high scientific and financial reputation within the stock market then the result of such investment is likely to drive the share price of the biotechnology firm's stock upwards in response to the new information that such an alliance provides shareholders.

Just as pharmaceutical firms are seen as an independent auditor of the worth of biotechnology firm partner's Exploration projects, large high reputation firms in other sectors could fulfil the role of technological and commercial auditor of the value of Exploration projects in small, relatively young, firms in their sector. Should they confirm the potential value of a project in a small firm by investing in the project, then shareholders uncertainty about the likely success in the management of the R&D project and its eventual commercial value should be reduced. In this circumstance one would expect the small firm's share price to rise in response to a reduction in uncertainty over the future success of a major Exploration project. Both firms gain from the partnership. The large firm obtains access to new technologies and processes without incurring the risk or cost of initial Exploration. The small firm gains access to world class development and commercialisation capabilities and the validating effect that the alliance may have in the eyes of its shareholders.

Should firms in other sectors seek to engage in prestige alliances as a mechanism of not only gaining access to resources and capabilities that they lack, but also seek to obtain reputational benefits then it is important that they select partners carefully. The management of the smaller firm need to ensure that the due diligence benefits that occur in prestige alliances in the biotechnology sector can be recreated in their own. Questions that need to be asked include whether or not the alliance partner will have access to scientific and commercial capabilities necessary to value the project? Are the scientific and commercial capabilities of that partner widely respected within the stock market? Will the audit undertaken by the partner signal uncertainty reduction information to the stock market in a more credible manner than prior announcements

by their own firm? Is the intellectual property embedded in the collaborative project sufficiently protected to ensure that the smaller firm will be able to extract value from a successful project? In the case of biotechnology/pharmaceutical alliances the existence of strong intellectual property rights, through the patenting of compounds, helps ensure that the biotechnology firm can demand a share of eventual royalties. Such patents confer on the biotechnology firm legally enforceable rights. The biotechnology firm's tacit knowledge about the workings of the compound also ensure that it plays a role in on-going discovery and development, thus again enabling it to maintain a share of value. Thus the biotechnology firm is able to protect some of its explicit and tacit knowledge from sole appropriation by its partner.

If the answers to the prior questions are all yes and the smaller firm is able to ensure an on-going role in the value creation and appropriation process then formation of alliances with prestige partners may be an important value creation activity in sectors outside the research focus of this thesis. Prestige alliances have facilitated considerable investment in Exploration within the biotechnology sector, enabling such firms to avoid the tendency of Exploitation investments to drive out Exploration. These alliances have also been of considerable benefit to large pharmaceutical partners, enabling them to participate in a wider range of innovative projects than would be otherwise possible. The application of such alliance networks in other sectors may act as a powerful stimulus to investment in Exploration activities, encouraging creation of innovative new products and processes, and avoiding over investment in Exploitation activities, thus improving the long term ability of firms to survive in turbulent environments.

TABLE ONE: EVENT STUDY HYPOTHESIS REVIEWED

Short hand version of Hypothesis ⁴³	Number of Events	UK Bio Percentage ARs	Significance	Avg. Returns Percentage ARs	Significance	Hypothesis Supported?
1. Announcement of alliances has a positive effect on share price.	31	7.5	Parametric: $p < 1\%$ Non-parametric: $p < 1\%$	7.9	Parametric: $p < 1\%$ Non-parametric: $p < 1\%$	Strong support
2. Announcement of Prestige Alliances has greater positive effect than Regional Alliances.	Prestige: 15 Regional: 16	Prestige: 10.1 Regional: 5.1	<u>Prestige</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Regional</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Prestige: 10.0 Regional: 5.4	<u>Prestige</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Regional</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Strong support
3. Announcement of R&D progress has a positive effect on share price	24	6.6	Parametric: $p < 1\%$ Non-parametric: $p < 1\%$	7.2	Parametric: $p < 1\%$ Non-parametric: $p < 1\%$	Strong support
4. Announcement of PII/PIII trials will have a greater positive effect than Discovery/PI trials.	PII/III: 16 Discovery/PI: 8	PII/III: 8.6 Dis./PI: 2.7	<u>PII/II</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Dis./PI</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	PII/III: 9.4 Dis./PI: 2.8	<u>PII/II</u> Parametric: $p < 1.0\%$ Non-para: $p < 2.5\%$ <u>Dis./PI</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Medium support
5. Announcement of alliances has as positive an effect as R&D trials	Alliances: 31 R&D: 24	Alliances: 7.5 R&D: 6.6	<u>Alliances</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>R&D</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Alliances: 7.9 R&D: 7.2	<u>Alliances</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>R&D</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Strong support
6. Hierarchy of announcement effects from Prestige Alliances, PII/III, Regional Alliances, to Discovery/PI	Prestige: 15 PII/III: 16 Regional: 16 Discovery/PI: 8	Prestige: 10.1 PII/III: 8.6 Regional: 5.1 Dis./PI: 2.7	<u>Prestige</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>PII/III</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Regional</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Dis./PI</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Prestige: 10.0 PII/III: 9.4 Regional: 5.4 Dis./PI: 2.8	<u>Prestige</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>PII/III</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Regional</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$ <u>Dis./PI</u> Parametric: $p < 1\%$ Non-para: $p < 1\%$	Medium support

⁴³ For a complete statement of each hypothesis the reader is referred to the Theory and Hypothesis section of Chapter Four.

TABLE TWO: SUMMARY OF IMPLICATIONS

Statement	Evidence	Implication(s)
Temporarily distant Exploration activities can add observable shareholder value.	<ul style="list-style-type: none"> ▪ The financial renaissance of Celltech (Chapter Three) was underpinned by a major shift towards investment in Exploration projects, in particular the CDP 571 Septic Shock project. ▪ Exploration events yield an abnormal return of 2.7% (Chapter Four, Table Seven, UK bio model). The event effect for individual Exploration events can be very large (Chapter Four, Table Twelve). For example, Chiroscience jumped £ 15 million based on entry of one project into Phase I clinical trials. 	<ul style="list-style-type: none"> ▪ Renewal is possible via increased investment in long term Exploration projects even in financially hostile environments. ▪ The quantifiable effect that announcements of progress in Exploration have in the stock market shortens the feedback loop between Exploration and financial performance. ▪ This challenges past theoretic suggestions in the Exploration/Exploitation literature that feedback loops between Exploration and financial performance are long and casually complex.
Performance of small listed companies can offer benchmarks for valuation of Exploration and Development projects in larger firms and the recognition, or reward, of key staff.	<ul style="list-style-type: none"> ▪ Chapter Four observed significant increases in market capitalisation of small firms, generated by announcements of progress in their Exploration and Development projects. Such effects, while large in terms of single projects, may be too small to observe within large firms with market capitalisations in the thousands of millions of pounds. 	<ul style="list-style-type: none"> ▪ Large firms with many Exploration and Development projects may not be able to identify an announcement effect of progress in each project in their own share price due to confounding effects and very large market capitalisation. ▪ They could track Exploration projects in small firms and use the observed announcement effects to partially value similar projects inside the large firm and reward staff based on these market valuation proxies.
Alliance formation plays an important role in signalling the value of Exploration and Development activities.	<ul style="list-style-type: none"> ▪ All alliances yield an abnormal return of 7.5%, while prestige alliances yield an abnormal return of 10.1% (Chapter Four, Tables Two and Three, UK bio model). Most alliances involved Exploration and Development projects. ▪ The Bayer alliance on CDP 571 was central to Celltech's financial renaissance (Chapter Three). 	<ul style="list-style-type: none"> ▪ High reputation partners have access to information about specific projects and scientific and commercial capabilities in auditing the potential of such projects that the market may lack. Their decision to participate in such projects is valued by the market as it contains uncertainty reduction information. ▪ Selection of partners should not be dependent on the resources they bring to the project alone, but also the reputation effect.

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Appendix One

THE CELLTECH CASE STUDY:

Celltech's Rejuvenation in the 1990s

INTRODUCTION

Celltech was born in 1980. Investment funds were obtained primarily from British and Commonwealth, Midland Ventures, Prudential and the British Technology Group. From 1980 to 1990 the company built up the foundations of a strong contract manufacturing and development business, in addition to an in-house research and development business. In the early years the firm had a diverse set of interests focused around diagnostics, nutritional and contract business. Only towards the end of the 1980s did it begin to focus primarily on therapeutics (drugs for human consumption) including involvement beyond sub-contracting. Its key technologies were the large scale production of animal cells and hybridomas and their use to produce monoclonal antibodies. Management's goal was to cover the costs of developing in-house drugs with revenues generated from contract work. Even though it seemed to succeed in this goal, shareholders were unhappy: Celltech had only one product in clinical trials, an osteoporosis drug. The largest shareholder was in financial difficulties and needed to realise its investment. Other investors wanted to remain with the firm, but were unhappy with the status quo. They wanted the firm to have more candidate drugs in trials and increased research productivity.

In 1990 Dr. Peter Fellner joined the firm as the new CEO with a different perspective. He saw the future in the collaborative development of innovative drugs with major pharmaceutical partners. These new collaborations would differ from the contract research of the past because Celltech would share some of the risk and rewards if the product came to market. As he puts it, "the winners have to be the companies in therapeutic because the value added is so huge." From 1990 to 1996, the firm re-focused its efforts on creating a capability in the development of innovative drugs.

These drugs were to be developed up to phase III clinical trials. All projects were to be in the therapeutic areas of Immunomodulation, Oncology and Inflammation. This strategy posed new technical and organisational challenges to the firm. The principal technical challenge was to create new capabilities in biology and medicinal chemistry, moving from a technological focus towards the development of drugs. The organisational challenge that this posed was to shift away from hierarchical research towards inter-disciplinary in-house research.

In 1990 contract manufacturing and development was made into a separate company, known as Celltech Biologics. In 1996 the Biologics firm was sold for £ 50 million to the Swiss firm Alusuisse-Lonza. By this action Celltech pinned its flag firmly to the mast of R&D in innovative drugs to advance human health.

Celltech (in 1996) had a market capitalisation of over £ 400 million, making it one of Britain's largest independent biotech firms. It invests over £ 17 million pounds a year in R&D. With over 180 employees it is large, even by US standards. It has over five drugs in clinical trials and a further five or more in pre-clinical development.

By the end of 1996 Celltech had a strong financial position in the UK biotech sector. The sale of Biologics and cash payments from alliance partners had reduced the need to rely on capital markets as a sole source of funding. The company had a senior management team that had considerable experience in the pharmaceutical and biotechnology sector. It had created a strong portfolio of discovery and development projects, in partnership with some of the world's leading pharmaceutical firms. Now it was at a pivotal period in its history, with its first potential product on the brink of regulatory approval.

THE EARLY DAYS: CRISIS, A NEW TEAM, AND A NEW MANDATE

The Emergence of a Crisis

In 1988 the *Financial Times* included Celltech in its 'pick of the British and US firms specialising in therapeutic drugs' (Science Editor 1988). Yet in October 1989 the CEO

announced that he was seeking retirement (March 1989a) and by November 1989 the *Financial Times* was identifying Celltech as a potential take-over target (March 1989b). It was a crisis in shareholder support that prompted the arrival of a new senior management team and a major change in corporate strategy. In the years leading up to this crisis while the firm was not making strong profits neither was it a loss maker (see Table One for financial details). Considering the biotechnology sector in general Dr. Fellner noted, in 1996, that:

“the shareholder loyalty issue is tightly related to financing risks. As shareholder loyalty declines the cost of capital rises. This is particularly important in the biotechnology industry which is such a large consumer of capital at present and does not have access to cash-flows from product sales as yet.”

Interpreted in this light the events of 1989 are quite significant.

INSERT TABLE ONE ABOUT HERE

The first real public warning of trouble seems to have been signalled by an article in the *Financial Times* suggesting that Celltech might be a take-over target prompted by an announcement in 1989 that British and Commonwealth wished to sell its 36.4 % shareholding (March 1989b; Celltech Annual Report 1989). The pressures in B&C were mounting and these were passed on to Celltech. At this time Celltech was not quoted on the London Stock Exchange. Although shares were transacted by means of matched trading this mechanism was really an avenue for exit by small investors, rather than one the size of B&C. By mid 1990, B&C had gone into administration and needed to realise its investment. A difficulty was that the market value of Celltech had remained relatively static over the previous two years (March 1989b, 1990b).

According to a member of the current management team attempts during the period of crisis to convince a pharmaceutical company to buy the B&C stake proved difficult as those approached seemed to value the company at below the price at which the original shareholders had entered the company. This view is reinforced by a contemporaneous article in which a number of senior executives in pharmaceutical firms stated they were

not interested in buying Celltech because they did not believe the firm would (at that time) add value above its price (March 1990a). One analyst noted in the article that “anyone who buys Celltech will be buying an enormous amount on trust.”

The B&C crisis was not the only issue facing the firm. One of the current senior management team recalls that in 1990:

“The company was in a fairly parlous state because a number of projects that had been much vaulted by the previous management had not delivered as much as had been hoped.”

Dr. Fellner notes that generally diagnostics and contracting had tighter margins than those achieved by firms who were successful in drug discovery and development. In his view the greatest upside potential in the sector exists in the discovery and development of novel drugs, hence the new strategy of focusing on drug discovery and development rather than on the other options. This required a change in strategic focus. The change in strategy was influenced by the demands of current shareholders, the desire for change of many within the company, as well as by the ideas of the new management team.

Shareholder’s desire for change was, to some extent, mirrored by internal desire for change. According to Dr. Ursula Ney, who is now the Director of Development but in 1990 was a project leader, inside the firm was a growing acceptance that a change in corporate direction was needed. Reflecting on 1990 she noted:

“In the months leading up to the change I think a lot of people had seen that the company was in trouble. Partially there were people coming up for retirement. The head of research was due to retirement as was the CEO and others. The company had lost its focus, it had lost where it was going. The majority of people realised that something had to be done.”

The appointment of a New Team

The company and the shareholders were looking for an experienced management team who could be trusted to direct a new approach. In August 1990 it was announced that Dr. Fellner had been appointed as the new CEO and that Dr. David Bloxham, who had worked with Dr. Fellner in the past, was appointed as the Director of Research (*Financial Times* 1990).

Recalling the mood at the time one of the senior management said:

“It was relayed to us by the original investors that ‘you are smart guys. You can tell us a nice story, but how do we know its valid?’ You see six or seven years ago very few financial institutions knew anything much about science, let alone the pharmaceutical industry and they felt that they had already been *hoodwinked* by one group of management and so what they said was we had to do something quite distinctive that made them believe there was something special about us.”

The experience of the new team, which took up the challenge of the shareholder, is given in Table Two.

INSERT TABLE TWO ABOUT HERE

Shareholders and the New Mandate

Dr. Fellner believes that over the long term shareholders invest in Celltech because it has:

1. The expertise and ability to deliver therapeutic innovations;
2. The ability to judge when and how much to invest in R&D options and to remain focused around these investments; and
3. An ability to communicate effectively with the city in terms it understands.

It is left to the reader to determine from the remainder of the case whether this long term perspective was balanced against the short term stipulations laid out by the

shareholders. Dr. Bloxham, the current CEO of Celltech Therapeutics, recalls that these were threefold:

1. To make no new share issues in the short term:
2. To improve the liquidity of Celltech shares through flotation on the London Stock Exchange; and
3. To strengthen the share price and reduce losses from therapeutics.

Within these three criteria the management had a carte blanche. The key for the new management was to increase the value of the firm such that shareholders could make some capital gain. Given the valuation problems, sale to a third party was not a viable option (March 1990a).

One senior manager noted that the new management needed to build on the fruits of the first ten years of therapeutic discovery, while carrying along sufficient internal support to implement change. Reflecting on 1990 the same executive recalled that the previous management had left the company with some considerable advantages. The firm had

“been quite successful at times during the 1980s and the management had raised something like £ 70 million from the market, which in those days was not trivial. They had created a manufacturing business that was, apparently, running in a reasonably profitable manner. What this meant was that when we arrived on the scene we had quite a positive cash balance ... {however}⁴⁴ ... the original investors were malcontent and had a number of stipulations on what could be done.”

As noted earlier, Dr. Fellner views shareholder loyalty and confidence as critical to UK biotechnology firm’s survival. Without shareholder loyalty Celltech would have no ready access to the capital markets. The firm was years away from product generated

⁴⁴Items in {} are interpretations of what the interviewee meant rather than exact quotations.

cash flows, and had cash burn⁴⁵ of only two years. In the view of several senior managers there was an urgent short term need to control expenditures and seek alternative sources of income, while simultaneously creating a strategy which would reduce short term shareholder dissatisfaction and raise long term market confidence.

Re-structuring

The primary short term priority of Celltech's management was survival. Dr. Bloxham recalls that:

“The first issue we really had was to scale the organisation back to the size which was appropriate for the financial base of the organisation and our potential access to capital, which at the time looked rather poor.”

In pruning the organisation the two most basic tasks were to sub-divide the group into two separate firms and to re-organise R&D to be more productive.

The two new firms were Biologics and Therapeutics. Biologics was concerned with contract manufacturing and development services. Although it provided income, and overall profitability, this business offered little upside potential when compared with Therapeutics. The rationalisation of Biologics maintained it as a profitable, but separate business. Therapeutics was concerned with the discovery and development of novel drugs. No longer was Therapeutics to engage in contract research. Now it was to have long term participation in all R&D undertaken. From an outsider's perspective, this restructuring complemented the efforts to increase productivity and to reduce costs through clear delineation of tasks between the two firms.

The overall R&D expense was reduced (see Table One) while actions were simultaneously taken to make research more product focused. Some savings came

⁴⁵Cash burn is taken as the amount of cash and equivalents on the balance sheet divided by the pre tax losses of the firm. It is a rough approximation of how long the firm has before it will need to return to capital markets or seek alternative sources of finance at its present rate of income and expenditure.

from a reduction in open ended academic collaborations. A senior executive remembers that:

“the company at the time I joined {in 1990} had a lot of open ended collaborations {with academics} in fact almost a third of its R&D spend was on these collaborations. I can say that almost universally they were very non-productive. They were quite a cash drain on the company. We were almost ruthless in pruning these down ... The minute we were working on a two year time scale the open ended collaboration just didn’t fit into our time scales. There was no point in saying ‘well we are planning for what we will be doing in the year 2005’, when we were dead in 1992”

There was a simultaneous hiring of new staff and re-focusing of R&D activities. The immediate financial result of re-organisation was redundancies of 60 staff and restructuring charges of nearly £ 5 million (see Table One for financial details). R&D expenditure was reduced by £ 1.5 million and group losses halved. The cash burn now stood at 3.5 years and breathing space had been created.

THE EMERGENCE OF A NEW STRATEGIC FOCUS

The renaissance of Celltech’s standing in the city and the industry is inextricably linked to a new direction in the firm’s drug discovery and development strategy. The search for a research focus was strongly influenced by Dr. Fellner’s general view of the biotechnology sector that the margins in contract manufacturing and development, agro-bio, and diagnostics were slim. His interest was in the quest to discover novel drugs. If Celltech discovered and patented a major new drug it could get a twenty year exclusive right and the margins from this seemed to be huge when compared with the alternatives.

The choice of new therapeutic focus and organisational hierarchy was driven by the new top management. As Dr. Yarranton, who is now the Director of Research, put it:

“It came from the top. Of course there were managers further down but the way we were going to organise ourselves came from David Bloxham.”

The core of the new strategy was to have more product focused research Dr. Bloxham recalls that the change in overall strategy in 1990 was, in essence, a change in attitude.

“An organisation of this type is not judged by the output of scientific papers. It is actually judged by its ability to come up with technologies which in turn will lead to therapeutic entities. The technology itself is fairly valueless until you convert it into something practical ... What I think we emphasised, if anything, was to say that if that is the basis on which we are judged, then clearly if we cannot convert our technology into practical realities we will be complete failures. ... We felt we had to pick novel mechanism based approaches that gave us opportunities in areas where there was a clear clinical need to produce something which would be commercially worthwhile.”

Dr. Yarranton, sums up the change in broad strategy by saying:

“What happened when management changed was we said we are not going to do any more contract research. Research is here to generate products and that’s where ultimately the company will sink or swim. Contract research kept us going from year to year but it isn’t going to turn Celltech into a big pharmaceutical company or even give us a rosy future.”

People within the firm had come to refer jokingly to Celltech as the ‘University of Slough’. There was a consensus amongst the researchers that change was necessary. Both shareholders and scientists were looking for leadership. A number of senior executives noted that it appeared that the scientists inside the organisation wanted the new management team to make the choice of targets and rejuvenate the firm. Within the three broad areas of Immunomodulation, Oncology and Inflammation, the senior management decided to focus on five projects. There was a wide choice of target projects to choose from within the firm, however some of this research lacked a product focus. As Dr. Ney put it:

“I think that some of the decisions that we had to make were fairly obvious. We were under time pressures. We had to work quickly to start producing products and pipelines of products. So we couldn’t start with a blank sheet of paper.”

The choice was not dictatorial. It did involve consultation with the senior scientific staff. Thinking on the 1990 changes Dr. Bloxham puts it best when he notes that:

“The choice was not based upon randomly saying, ‘I will force everyone to do what I tell them to’. It was based on saying, ‘I think these are the twenty best people in the organisation. These are the ideas that they would be most comfortable with. We will encourage them to pursue those.’ Those individuals then gave the impetus to carry out the plan ... At the end of the day it would never be quite sure who came up with the idea {of each specific project} because I think it is a shared experience where you have to get all the scientists to buy into the project. One thing you learn very rapidly is that you can’t tell a scientist what to do in authoritative mode!”

Dr. Ney confirms this non-random selection process. She remembers clearly that Celltech were already making progress in cancer discovery, hence the focus on oncology. There was also a long running project in anti-TNF (Tumour Necrosis Factor), hence the focus on Inflammation and Immunomodulation. Dr. Bloxham had considerable past experience in Asthma projects, hence a new project in Asthma. The Asthma project also required a significant medicinal chemistry capability to be developed.

So while there were 60 redundancies, simultaneously 35 medicinal chemists were brought into the firm. This new blood not only provided key skills needed to implement the new strategy, but also a group of people who could stimulate and challenge Celltech with new ideas, uninfluenced by its past history. (This perspective may have been influenced by similar experiences which Dr. Bloxham and Dr. Fellner had encountered in Roche). The willingness to broaden the technology base in pursuit of the firm’s broader goal is a striking illustration of the change in strategy away from a technology focus⁴⁶.

⁴⁶ We mean by technology focus that Celltech had previously been driven by the development and maintenance of a technological expertise in large scale production of animal cells and hybridomas and their use to produce monoclonal antibodies to order.

RE-ORGANISING TEAMS FOR SCIENTIFIC CREATIVITY

Inter-disciplinary teams

Hand-in-hand with the selection of a new research focus was the re-organisation and strengthening of the process by which new scientific knowledge was created and applied in the firm. In 1990 teams in the firm were considered by Dr. Bloxham to be over staffed. There had been an assumption that satisfactory research productivity could be achieved by organising around separate departments within which resided homogeneous functional specialists. The new strategy considered a key lever to improved research productivity to be a focus on medicinal indication rather than functional specialism (e.g. Cell Biology; Biochemistry). Research teams were therefore re-organised around specific indications and diverse specialists were brought together to work on that specific indication. The value of all research was to be measured in terms of production of new drug candidates. The principal was that each research team would now have sufficient resources and capabilities *within itself* to develop plausible drug candidates in their targeted indication. The stand alone teams now had both critical mass and strong research focus, yet the numbers of research staff remained largely unchanged.

The re-organisation involved moving the firm from an extremely hierarchical form, in which researchers each worked in relative isolation within their specialist departmental areas, to a flatter structure. The old organisational form had created a strong technological focus and capability, but if Celltech was to develop novel drugs it had to strengthen its capabilities in biological research.

In commenting upon the Celltech of 1988 Dr. Ney, who was then working as a project manager in the firm, noted that:

“I must admit that when I first came here I was amazed that the organisation of research was skill based, which in some cases consisted of departments with just two people ... For a very small company it was very hierarchical.”

Reflecting on the 1990 strategy change Dr. Geoff Yarranton, the Director of Research, remembers that the move from hierarchical towards interdisciplinary research:

“was really almost a sea change in the way that we were organised...”

Motivating Scientists to Change

Motivating the scientists to embrace change seems to have been an important theme. Several senior executives commented that if change was to succeed it was critical that the scientists supported the re-organisation. Without their co-operation the firm could not hope to change its course and take a compound quickly from discovery into development. To make these new teams work Dr. Bloxham believed that it was critical to communicate clearly that the focus of the scientist's job had changed away from development of technologies and towards production of products, which by necessity involved interdisciplinary inputs. As he put it:

“What really was required was to make the scientists themselves understand that what they were being judged on was products entering into clinical evaluation rather than the development of technologies per se. It always seemed to me that all that was needed to focus this energy {the creative energy of the scientists} was to make them all believe that what they are here for is the improvement of human health and if that's what they are really interested in they can only do this by having products which do something about it.”

Dr. Bloxham's point is reinforced by Dr. Ney who remembers that:

“Having a bit of a clean out and starting again (looking back) was quite well accepted. It hurt some people, there were a lot of redundancies {in Biologics} but that didn't really affect the therapeutics side ... Therapeutics was fairly untouched in the harsh numbers game that was being played. They had to change their type and style of work, but I think that a lot of people liked it.”

Dr. Yarranton shares this view, noting that the change, in and of itself, was a great motivator as it offered scientists a new challenge, something which, in the right environment, they relish. Reflecting on the 1990 change in strategy he says:

“It was quite invigorating that change because it was such a big change. I think when new management comes in it is quite good to make a significant change. It gave people a new challenge, because they were challenged with learning more about the biology, rather than just learning about techniques and technology ... People hunger after challenge. Obviously some people left because they didn’t like it, but in general we didn’t have that much turnover. People could understand the rationale. Obviously the rationale was that we need to get products, and to get the products you need to understand the biology of the systems. They were organising these models into biology focus groups {focused around the three therapeutic areas and including medicinal chemistry capabilities}. People seemed to enjoy that {working in inter-disciplinary teams focused on developing drug candidates in one indication}. There was a buzz about the place, and it was quite new.”

Inter-disciplinary Learning

An environment of inter-disciplinary co-operation regarding knowledge sharing and creation was fostered in Therapeutics. Thrown together and strongly motivated by crisis and shared vision, researchers had to learn to work together on a common task. Formal interdisciplinary interaction was reinforced by informal socialisation. The labs at Celltech are open plan, with coffee and dining areas near the labs, which may help in the creation of proximity.

The new tasks often involved researchers moving out of their own specialist field, learning new skills, blending these with their own, and through this creating a broader based shared language with which to interact with their colleagues. Thrown into this cauldron were the newly hired medicinal chemists. The new people faced the informal social and professional ‘clubs of the old.’ The ‘old clubs’ faced yet another uncertainty - new people with a different language and knowledge base.

Dr. Yarranton says that tensions between these groups took time to reduce and total integration has not yet been fully achieved by 1996. The process of learning to work

together created a new knowledge base and capability within the firm. Dr. Yarranton sums up this transformation in working methods and capabilities when he says that:

“We were very much organised along technical disciplines for quite a long time which gave us a very good strength in technology but maybe not a good strength in biology. We found that when we moved into the therapeutic areas that we were able to get people to be focused on biological questions so that they built up their biology base. So we had people who have a lot of interest in inflammation and these people built up a knowledge base around inflammation as opposed to being molecular biologists, or cell biologists, or biochemists.” The re-organisation “challenged {researchers} with learning more about the biology, rather than just learning about techniques and technology.”

Dr. Bloxham believes that the net result of these changes in teams and research focus enabled Celltech to have sufficient mass to undertake big, liberated science. This motivated the scientists and enabled the group to push products quickly through the discovery process into development where they could be used to attract collaborators.

THE NEW STRATEGY IN ACTION: THE BAYER COLLABORATION

The principles of the new strategy can be understood by examining the story of CDP571/BAYX1351. At an interview in 1996 Dr. Bloxham noted that this project was an interesting example of the Celltech strategy in action. He commented that:

“it highlights both all the successes and the problems that go with a business of this type ... I think that it is an interesting project to focus on because it will tell you just about everything you need to know about the roller coaster life that exists within the biotechnology sector.”

Selection of the Project & early days

The story begins in the labs of Celltech during the mid to late 1980s. The firm had been working on a murine based antibody to TNF (Tumour Necrosis Factor) as a therapy for Septic Shock. The R&D of this product had been proceeding well and the firm had several strong patents filed protecting its anti-TNF position. In 1989 Celltech

decided not to develop the murine product because management believed that the time lags to market were too long. Consequently it began a recombinant programme to humanise the murine antibodies. The humanised product would be a more advanced product.

In 1990 the winds of change transformed the fortunes of anti-TNF programmes in Celltech. The new management were looking for a programme from which they could show quick results to the market and found one in the shape of CDP571/BAYX1351. The new senior management believed Celltech had to get something out of the labs quickly to attract a major pharmaceutical collaborator. In the view of Dr. Bloxham such a collaborator which would provide the company with cash payments, to reduce the rate of cash burn, and validation in the eyes of the capital markets. The two year cash burn did not give much time, therefore a fairly advanced programme needed to be found quickly. As he put it:

“We wanted to {get the project out of the laboratory and into development} in the shortest length of time possible because we wanted to use that as the basis of a collaborative deal we would do with somebody and that would be our validation. That validation would enable us to raise more money and survive. So a lot of what we did with that project is linked to the process of survival and evolution of this business and the satisfaction of what shareholders wanted which was an increase in liquidity and a better share price.”

Dr. Ney believes that anti-TNF was chosen because:

“There had already been a research programme {CB-6} in Celltech to look at engineering an antibody. So some of the ground work had been done. It was sitting there and could produce a product in terms of engineering an antibody. We had a lot of the skills in-house to do that. People knew what they were. You could see how you could, in a limited space of time, get a product through.”

Dr. Yarranton, who had been leading the earlier anti-TNF projects, believes that the central additional ingredient new management brought

“was to look not only at Septic Shock and say ‘well maybe things like Rheumatoid Arthritis and immune diseases are a better target than Septic Shock’.”

Collaboration - Making a Deal

The massive effort of CDP 571 began to show quick results. The drug candidate started moving out of the labs and into development in the summer of 1990. This coincided with the firm’s search for a collaborator and it quickly became apparent that Bayer was a suitable candidate. Bayer met Celltech’s requirement that the collaborator be a major pharmaceutical firm. Combined, the firms could command what Dr. Yarranton believed was an “almost impregnable position around TNF.”

At that time it was believed that Bayer’s murine anti-TNF for Sepsis was close to a successful phase III trial. Celltech agreed to halt its own humanised programme in return for a share in the future rights of Bayer’s anti-TNF project. The collaboration proposed that the development of the next generation humanised product would also be undertaken at a later stage. Celltech would have responsibility for development to phase II with Bayer taking over there afterwards. Bayer would pay Celltech a potential £ 26 million in milestones. By the end of 1996 Celltech had received £ 15.6 million in milestone payments from Bayer. If the clinical trials proved successful Celltech would receive a 12% royalty on all sales by Bayer while retaining some European marketing rights (Lister 1996). Bayer calculated that the potential peak market would be \$ 700 million per year, world-wide. From the shareholder’s perspective this was a deal with a major pharmaceuticals firm, and thus a validation of Celltech’s long term potential value. From the view point of those inside the firm the success in getting a product out of the clinic and into development, in addition to enlisting a major collaborator, may have signalled that the new management’s strategy was beginning to show tangible results.

Learning and Adaptation from CDP 571/BAYX1351

During 1996, while reflecting on the Bayer collaboration, Dr. Bloxham noted that lessons were learned which were applied to the later, post 1992 collaborations. Dr.

Ney noted that the collaboration was a lesson in the inner workings of large firms, the uncertainties of clinical trials, and the challenges of co-operation. Bayer's first phase III Sepsis trials proved inconclusive and hopes of a quick product to market dissipated.

In the early 1990s, awaiting results from Bayer on the Sepsis phase III clinical trials, Celltech independently funded clinical trials into two additional targets: Crohns and Rheumatoid Arthritis. In retrospect, the logic, according to Dr. Bloxham, was that:

“We had a deal which was based entirely on Septic Shock. We could have stopped there completely ... {however} we felt there were more opportunities for this malady that we would want to explore, therefore we undertook to explore them at our own expense. We were hoping that we would generate results which would be good enough to convince Bayer that in addition to the work on Septic Shock they should contemplate expanding their research activities ... this was clearly a management decision.”

The idea was that if the eventual Septic Shock trials proved unsuccessful then Celltech had another promising route which it could develop quickly. If the Septic Shock trials proved positive then these candidates could be pursued to reinforce the collaborators position in the anti-TNF market. In Dr. Bloxham's view this offered Celltech “an each way bet.” These trials were successful up to phase II. In an agreement with Bayer the phase III development of these candidates was passed over to them, thus conserving Celltech's cash positions.

The decision to proceed first with Septic Shock, followed later by Rheumatoid Arthritis and Crohns Disease, was, according to Dr. Bloxham, due to “a genuine market issue” of which market and product to develop first. For complex market reasons Bayer needed the Septic Shock drug to be developed and released onto the market first. Furthermore, the view of Peter Allen, Celltech's Finance Director, is that were Celltech to have developed successfully a treatment for Septic Shock it would be of greater financial value than one for Rheumatoid Arthritis, though both would, of course, be substantial.

At present there is no drug treatment for Septic Shock on the market, thus if Celltech were to succeed in developing such a drug it would be the first player in this market. About a half a million people per annum suffer from Septic Shock, which is often fatal (Celltech Annual Report 1995). About 800,000 people per annum suffer from severe Rheumatoid Arthritis (Celltech Annual Report 1995). There are a number of drug treatments for this illness already on the market. From the point of view of the management Celltech would be a second mover in this market and could not expect to capture as large a market share as in that for the treatment of Septic Shock

In 1996 Dr. Bloxham commented that the difficulties of 1990 meant that Celltech could not take on much risk, hence most of the later development costs and responsibilities were passed over to Bayer. Now (in 1996) that Celltech is financially stronger and has enhanced skills, internally and through collaborations, he believes that a greater load of risk, for increased returns, could be borne. Dr. Bloxham believes that if the Bayer collaboration were to occur today Celltech would seek to take a greater proportion of the discovery and development process, thereby retaining more control over European development and marketing and a greater proportion of final rights. This would probably involve a lower proportional milestone payment. According to some members of the Celltech management team such an arrangement would allow Celltech to work jointly with, but not be completely reliant on, the sometimes slow, though undoubtedly methodical, progress of major pharmaceutical firms. Celltech's speed in clinical development within European markets could be used to show slower collaborators the way and to spur faster progress. This would shorten the time taken to get through clinical trials while retaining the marketing and phase III clinical trial expertise and resources brought by large collaborators.

The financial result of the project was startling. By the end of 1996 Bayer had paid £ 15.6 million in milestones, none of which was repayable if the project eventually failed. In 1996 Dr. Bloxham summed up the value of the Bayer collaboration:

“it was a very cash positive deal. It gave us a lot of kudos in the city. Bayer is a highly respectable company and they will get products out of the deal if there are products there”.

The logic of collaborator validation appears to have been vindicated by later press comments, one of which noted:

“Most importantly, Celltech has collaborations with big name drugs companies and their expert assessment is worth more than a City analyst’s report. Where companies such as Merck, Bayer and Schering-Plough invest, others follow.” (Green 1994a).

BUILDING ON EARLY COLLABORATIVE SUCCESS

The CDP571/BAYX1351 project was not without its risks, both in terms of technique (anti-TNF) and choice of illness (Septic Shock). Anti-TNF is a novel but risky approach. In 1995 US biotech firm Immunex halted Anti-TNF clinical trials due to unpromising results. Furthermore, it has been reported that nine US biotech firms have targeted drugs at Septic Shock, but all failed in clinical trials (Lister 1996). Infamously, Synergen failed a phase III clinical trial on a Septic Shock. It chose to re-test while simultaneously building a manufacturing facility only to fail again. The result was a take-over offer by Amgen for Synergen that valued the firm at \$9 versus \$66 per share at its height in 1992 (Green 1994b). To manage such risks senior management at Celltech felt it necessary to develop additional promising projects with first tier collaborators. The firm proceeded to do this with considerable success.

In 1993 a new collaboration commenced with Schering-Plough, while an older collaboration with American Cyanamid successfully survived that firm’s merger with American Home Products. Further collaborative R&D deals were struck with Merck in 1994 and Zeneca in 1995. The reasoning behind these deals is compelling:

“Because of the high cost and complexity of world-wide product development and marketing the company collaborates with major pharmaceutical companies which possess the necessary technological expertise and financial resources to optimise the probability of success. As the company progresses towards profitability we intend to retain a greater proportion of European rights to new products” (Annual Report 1995)

The benefits of this strategy appear to have had a positive influence on the firm's image in the city's eyes (Green 1994a, c).

Figure One provides an outline of the collaborative ventures in which Celltech was involved in 1996. Essentially knowledge flows between the collaborators and in return a share of rights to future products, milestone payments and vital skills and resources are exchanged. Financially Celltech gains milestones payments. To date this has amounted to over £ 26.5 million, with a contracted potential of £ 83 million. Development costs which otherwise would have to be borne by Celltech have been passed over to collaborators. Dr. Yarranton estimated that by 1996 milestone payments from collaborators covered nearly 50% of research and development costs at Celltech. Milestones notwithstanding Celltech maintains a substantial share of the final rights of products sold. Royalties and rights accruing from collaborations are calculated to amount to between 25% and 45% of net profits.

INSERT FIGURE ONE ABOUT HERE

Celltech management noted that collaboration also validates the firm's worth in the city's eyes. Following this logic, the financial reward of the virtuous cycle of collaborative validation came in 1993 in the shape of the largest ever placing and public offer of shares of a biotechnology business in Europe. This helped strengthen the balance sheet by £ 30 million. It also reduced the firm's exposure to B&C's need to sell a substantial shareholding in Celltech, which had been one of the triggers of the 1990 crisis. While in 1992 B&C controlled about 36% of Celltech, by 1995 this was reduced to less than 4%.

Collaboration brings benefits, but it is not without resource allocation problems for Celltech. The collaboration with Merck acts as an illustration of these commitments. The project has moved from research and into clinical stages and back again. When work moves back into research up to 30 people can be assigned to that collaboration alone. These commitments vary in size, but continue to impact on resource allocation during the life of the collaboration.

Dr. Ney once commented that collaboration often means the firm must face a longer time to market. This is sometimes due to the slower speed of larger collaborators, to the time involved in knowledge transfer, and/or to systems differences. She points out that this has its risks. For example Centocor, Celltech's major rival in anti-TNF, were moving much faster through the regulatory process because they were working independently. They were also looking at Rheumatoid Arthritis and Inflammatory Bowel disease targets. One of the key questions Celltech faced was whether its technology would win through the regulatory process where Centocor's did not? In this case Celltech would be alone in the market. Alternatively, what would *happen if* Celltech's product, which Dr. Ney believed to be superior, arrived at the market later. In this case could Celltech, as a second mover, capture an increasing market share through both a superior product and employment of Bayer's deep marketing expertise and global distribution system?

SYSTEMS TO MAINTAIN MOMENTUM

From an outsider's view point it seems that underpinning Celltech's ability to generate sufficient progress in research and development to maintain and expand its portfolio of collaborators and drug candidates has been the establishment of new management systems. According to Dr. Yarranton these systems help monitor and review progress of current projects and identify and select new ones. Timely termination of failing projects is a key element in maintaining research focus and conserving scarce cash resources. For a new project to be given the 'go ahead' it must have clear quantifiable measures, based on clinical criteria, by which it can be managed. Termination and selection require both managerial insight and systems of monitoring and control.

Dr. Yarranton describes the monitoring process as follows:

"You manage the projects by objectives and milestones. All objectives should have time frames associated with them. You have regular quarterly reviews, after all, we are a small company so you can monitor things reasonably closely. So the bells should start if there is a problem because you are not hitting the objectives. You then analyse if it is something very critical that is causing you to not hit the objectives. {For example} Is it because there is a technical problem? I make a

judgement as to if it is solvable and if so how long is it going to take to solve. So that's really how we manage them. If there really is ... a problem that can't be solved we will of course terminate it."

Over the years the firm has installed four research selection, monitoring and review systems to maintain the momentum of its success. There are review systems for drug development, drug discovery, annual reviews, and long term strategic review systems

Research Review Systems

As products have moved out of research and into development with collaborators, research resources have begun to be freed periodically. This has placed an increasing emphasis on the selection of new research candidates. Ideas are always bubbling up from researchers, who are free to experiment on their ideas subject to two criteria. First, they continue to meet their job targets and second, with the proviso that experimentation does not place a significant resource drain on the firm.

As resources are freed the firm engages in both an informal and formal search for new candidates. As Dr. Yarranton puts it:

"You don't say that we are going to have a meeting on next Thursday. There usually is a lot of discussion about the ideas. Eventually they {proposals} come forward, but they don't come forward as a surprise on Thursday afternoon and we decide by the end of the day. Because we are a small company you are always talking to people so you have a good idea of what ideas are being discussed. It is almost a constant process of seeing what's new, what we might do, what's exciting."

Projects are more formally screened by a senior management team comprising the Directors of Research and Development, the CEO of Therapeutics and senior scientists. The following criteria are broadly applied:

- a) Does the project fall into the firm's three broad research areas ? If not, there would need to be an overwhelming benefit in entering such a project.

- b) Does the project proposal have a plausible clinical entity ?
- c) Are there clear quantifiable measures from which progress can be managed ?
- d) Does this project represent greater potential than competing alternatives ?

Development Review Systems

Reflecting on the early 1990s Dr. Ney commented that with so many products in the discovery pipeline the development process focused on taking products from research directly into development. This attitude has begun to change. The focus shifted towards research productivity. Staff are now expected to maximise the number of products entering clinical development. The central criterion for entry is that each product pass a Product Development Review conducted by a committee which asks a number of critical questions. Products that do not meet these criteria do not enter development. According to Dr. Ney some of the key questions are where is the market and what is the clinical need? It is not now simply a question of taking good research from the lab and into the clinic. The market pull dimension is growing in importance along side the supply push.

Projects must submit a Product Development Proposal (PDP) to the Product Development Review Committee before they formally enter the development process. This committee consists of all senior management with scientific expertise. It is an important aspect of Celltech's managerial systems that those who monitor and control project selection and review have the necessary practical scientific experience to make content and process judgements on project quality and performance.

The PDP identifies which issues will need to be addressed in the development cycle. These include the types of clinical trials to be run, and what are to be the clinical targets and clinical end points against which a trial is judged. Pre-clinical data is offered to support these statements. The 'market pull' factors are also considered with an analysis of the strength of the firm's patent position relative to the competition and a broad outline of the final market. Costing is included in the PDP. Prior to formal review of a PDP considerable informal discussions take place, hence no product

reaches the formal committee unless there is a consensus that it has a good chance of success in development. Of the six or seven products that have gone before the committee none have been formally rejected, but two have been subsequently dropped during development.

Annual Review Systems

The PDP review process is reinforced by a five to ten year rolling corporate plan that is undertaken each year. Under this annual process senior management compute cost implications of on-going and proposed projects. Senior scientists assess what targets can be achieved within the resource budget and present capabilities. Celltech has a policy that every project must be given enough resources to attain the milestones placed upon it. This differs from budgeting and review systems in some pharmaceutical firms. According to a senior Celltech executive one such firm applies a competitive system where achievement of last year's goals results in increased annual budget, and vice versa. This can result in a cycle of success for well funded projects and a cycle of ever deteriorating performance for struggling projects, as each setback is met with a reduced budget. Celltech believe that its policy is better than the competitive method which can lead to over-funding high profile scientists and projects, thereby reducing research efficiency.

Strategic Reviewing Systems

Every few years a more formal strategic review of the whole firm's research efforts takes place. In this review the firm reflects on where it is going as a whole versus where it should be going. As Dr. Yarranton puts it

“From time to time we do a more strategic review, rather than just saying everything is going fine and there is a slot now {for a new project}. Every so often we have to stand back and say, ‘are we doing things right? Has the game changed?’ About a year and a half ago we had such a strategic review. We decided that we would throw everything up in the air, without any preconceived ideas of what we should do. ‘What are the new areas we should be looking at ? What are the areas we have been working on in the last four or five years that should be changed?’”

Out of this review the firm did change some of its strategic objectives, which resulted in changes in projects and resource allocations. In particular there was a change in technological focus. Specifically, research commenced on expression of antibodies in microbial systems. This research is being carried out with the aim of significantly reducing the cost of goods in the future mass production of antibody products.

Despite strategic reviews the firm continues to have limits on the feasible breadth of change. The firm has committed considerable investment to past projects and skills. Naturally it is influenced by these capabilities in the search for new direction. Even in the considerable changes of the 1990s past decisions limited the choice of future paths. The leads for new projects in Celltech tend to come from the past. As Dr. Yarranton comments:

“It takes a lot of start up effort in medicinal chemistry programmes because you have to get all of you enzymes, your counter screens, your targets, you have to set a screen cascader. It is quite clear that there are NPTs {New Product Targets}.

This screening effort will help identify targets which the organisation can pursue now and which later may enter the regulatory approval process. In general, when seeking a starting point for a new project firms can return to the results of a previous screening effort in the identification of new promising drug candidate projects. As Dr. Yarranton observed:

“Your chemistry programme develops quite an interesting chemical bank in which you have some selection compounds and some non-selection compounds. The non-selection compounds are a good start for a chemistry programmes on other targets. So we can roll out from our own chemistry programmes additional targets without long start up times. Because all the agents are not changing, we can use the set counter screens. So there is a certain economy there that enables us to develop new drugs from existing projects.”

Introduction of new staff helps stimulate innovation and open up future paths of opportunity. Dr. Yarranton commented that

“{New staff} all have a different view, and some of these views maybe quite challenging. You always need to be challenged with new views. You do not want to just recruit people who take what you said and give it back to you - that's not very useful.”

The problem in the recent past is that staff turnover has been low. In research Dr. Yarranton believes that a turnover of 5-6% would be optimal, whereas currently it is about 3%.

According to a number of the executive team, the formal systems of PDP, Strategic Reviews, and Annual Reviews of the rolling plan, are reinforced by the informal consensus building approaches which are possible because of the firm's small size. Summarising the views of several executives one can say that these formal review systems are founded on the informal bubbling up of ideas and projects. The formal systems and tight quarterly monitoring of projects combined are the embodiment of a determination to identify and stop failed projects. These formal and informal systems are embedded in a culture of learning from failures within and across projects. Together this enables Celltech to identify promising projects and support them through the R&D process.

An overview of Celltech's principal, publicly quoted Research and Development activities is provided in Table Three. This puts some real drugs, diseases, and collaborators to the strategic developments that occurred between 1990 and 1996.

INSERT TABLE THREE ABOUT HERE

A BITTER SWEET PILL:

THE RESULTS OF THE SEPTIC SHOCK TRIALS

‘... it was found that in the patient group treated with BAYX 1351, mortality was not significantly lower than in the control group. The results do not confirm trends towards efficacy seem in two clinical trials on BAYX 1351’

Celltech Press Release dated 7 pm 20 May 1997

‘Celltech does not expect the second generation novel anti-TNF antibody CDP 571 (BAY 10-3356) to be further developed. Celltech now expects to regain the development rights for CDP 571 in chronic indications, including Crohn’s disease ... Celltech is financially very strong, with net cash at 31 March 1997 of £41.0 million. The company has collaborative agreements with a range of international pharmaceutical companies, and four novel product candidates in Phase II clinical development. In addition, it has a pipeline of novel compounds in pre-clinical development ...’

Celltech Press Release dated 7 pm 20 May 1997

The immediate market reaction the next morning was one of disappointment. On a day when the FTSE-ALL Share and FTSE Pharmaceutical indices rose slightly Celltech’s share price dropped dramatically from 630 pence to 341 at the close of business. About 45% of the firm’s market capitalisation was wiped out in one day. The market capitalisation fell from over £ 481 million to £ 260.5 million. Figure Two traces the history of Celltech’s share price since its launch on the London Stock Market. Despite the Septic Shock set back the market capitalisation of the firm was still higher than at the end of the first day it traded in 1993, when it was valued at over £ 176 million (all data from Datastream International).

INSERT FIGURE TWO ABOUT HERE

The termination of the Bayer collaboration was triggered by a clause in the collaborative contract. One senior executive commented that careful drafting of the original contract has been a vital lesson for Celltech. When the contract was drawn up it was recognised that the personalities and companies might change during its life, therefore it was important to draft the exit clauses tightly. This contract clearly stated that if the project were terminated for scientific reasons all rights returned to Celltech. This leaves Celltech with the option to obtain new collaborative partners, an option which it is actively pursuing.

No doubt had the drug passed Phase III then this would be an unqualified success story with a happy ending. Despite the setback the story is, however, one of success. Bayer

paid Celltech £ 15.5 million in milestones, yet the reported development expenditure incurred by Celltech was only 15% of that amount (Celltech Web site). The company has not lost its discovery investment. There are still several promising indications that CDP 571 may yet win through in terms of regulatory approval. Celltech is actively pursuing Phase II trials in Crohns disease and remains interested in Rheumatoid Arthritis.

To an outsider one of the key lessons of the Septic Shock story may be in the careful and realistic management of upside and downside risks in this highly risky business. Clearly this is an area in which Celltech excels.

In a recent article John Beary, the Senior Vice President of Regulatory and Scientific Affairs at the Pharmaceutical Research and Manufacturers of America, noted that only 5 out of every 5,000 compounds that make it to pre-clinical testing ever make it into human testing⁴⁷. Of those five only one is eventually approved. Seen in this light the Septic Shock programme did well to get as far as it did. With four other product candidates and a pipeline of pre-clinical candidates Celltech is still firmly in the race to realise its goal of taking drugs through from discovery into the market.

CELLTECH AND THE FUTURE

The financial strength, managerial experience, and product portfolio that Celltech has accumulated since 1990, means that it is well positioned in the UK sector. An analysis of Table Four confirms that Celltech is strong across a wide range of parameters compared with six of its leading peers listed on the London Stock Exchange:

- In terms of market capitalisation Celltech ranks fourth - this after a major setback.
- It has raised more from equity and asset disposals than all bar British Biotech..

⁴⁷ Beary, J. (1996). The Drug Development and Approval Process. *PhARMA Drugs in Development*.
[Http://www.phrma.org/charts/approval.html](http://www.phrma.org/charts/approval.html)

- It has the third highest cash burn. The cash burns for each of these firms has been calculated and it was found that Celltech has the longest with greater than 14.5 years, while the remaining firms are between eight and four years.
- It has the third highest number of staff, most of whom are in R&D.
- It has a very strong portfolio of major pharmaceutical collaborators when compared with the other firms.

INSERT TABLE FOUR ABOUT HERE

From the perspective of an outsider Celltech appears to have a strong position from which to re-group and base its future after the failure of BAYK 1351. It has learned a lot from its internal and collaborative ventures, building up a promising portfolio of potential drugs targeting diseases that affect large groups of the population. These projects each have partners with strong marketing and distribution bases on which future clinical trial success can be quickly turned into market presence. Its present cash position means that it can continue independent research for a number of years without recourse to capital markets. Overall Celltech has created a unique and strong position in the UK biotech sector.

TABLE ONE: FINANCIAL SUMMARY OF CELLTECH PLC

	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
	£ m	£ m	£ m	£ m	£ m	£ m	£ m	£ m	£ m	£ m
Turnover (biologics)	11.4	16.6	19.7	19.9	17.0	12.1	14.2	14.2	16.7	12.2
Cost of Sales				(14.9)	(12.6)	(7.4)	(7.8)	(7.5)	(9.5)	(8.5)
Administrative Expenses				(4.6)	(4.0)	(4.2)	(4.5)	(4.7)	(5.0)	(3.5)
Investment in R&D (biologics)	(3.4)	(6.0)	(7.9)	(12.1)	(10.6)	(12.0)	(14.8)	(16.2)	(17.1)	(17.4)
Investment in R&D (therapeutics)										
Milestone payments ⁴⁸ (therapeutics)	—	—	—	—	—	2.0	6.1	5.5	7.4	5.6
Operating Profit - Biologics	4.1	4.4	2.8	0.4	0.5	0.5	1.9	2.0	2.2	0.2
Operating Loss - Therapeutics	(3.4)	(6.6)	(7.9)	(12.1)	(10.6)	(9.8)	(8.7)	(10.7)	(9.3)	10.8
Group Profit/(Loss)	0.2	0.1	0.6	(13.4)	(6.7)	(7.4)	(5.9)	(6.9)	(5.4)	3.0
Net Assets:										
Fixed Assets:	11.4	15.4	19.1	14.7	12.8	12.8	13.5	17.4	23.7	12.9
Liquid investments, cash & cash equivalents	8.9	41.5	33.4	27.7	23.8	16.0	17.9	36.4	28.3	46.4
Long term liabilities	(1.2)	(0.6)	(0.06)	—	—	—	(0.2)	(0.4)	(2.4)	(0.5)
Financing: ⁴⁹										
Issue of ordinary share capital	—	42.2 ⁵⁰	0.08	—	—	—	—	30.0	—	3.2
Expenses relating to issue	—	1.6	—	—	—	—	—	(2.5)	—	—
Issue of preference shares	—	—	—	—	—	—	8.5	—	—	—
Sale & Lease back proceeds	—	—	—	—	—	—	—	0.2	2.6	—
Extraordinary items & charges	—	—	2.1 ⁵¹	4.96 ⁵²	—	—	—	—	—	31.4 ⁵³
Interest Income	0.8	3.0	4.1	4.1	2.9	1.85	0.9	1.8	1.7	1.7
Cash Burn years (approximation)	in profit	in profit	2.0	3.5	2.0	3.0	5.3	4.0	in profit	

Source: Celltech PLC Annual Reports 1988-1996. Celltech Web Site August 1997.

⁴⁸ By 1996 a total of £ 26.6 million in milestone payments has been received from collaborators.⁴⁹ The company raised a total of £108.9 million in seven separate financing rounds according to the Celltech Web Site, as at August 1997.⁵⁰ Pre 1988 the approximate funds from share capital were £ 27.8 million, with another £ 42.2 million in December 1987, according to the Celltech Web Site as at August 1997.⁵¹ Relates to the disposal of Celltech Diagnostics⁵² Re-organisation of Celltech into two separate firms: Therapeutics, dedicated to R&D of innovative drugs and Biologics, dedicated to contract manufacturing and development services.⁵³ Celltech Biologics was sold for a reported £ 50 million in the Summer of 1996.

TABLE TWO: BACKGROUND OF SOME OF CELLTECH'S EXECUTIVE TEAM

Name	Position in 1997	Position in 1990	Academic Background	Industry Experience
Dr. Peter Fellner	CEO of Celltech PLC	Joined Celltech as Managing Director in 1990.	PhD from Cambridge University.	Director of Research at Searle UK Research Laboratories. CEO of Roche UK 1986-90. Director of Roche UK Research Centre. Board member of British Biotech.
Dr. David Bloxham	CEO of Celltech Therapeutics	Joined Celltech as Director of Research in 1990.	PhD from the University of Southampton. Lecturer at University of Southampton in Biotech. Visiting Professor at University of Washington. Max Plank institute - Munich.	Director of Biology Research at Roche UK. Director of R&D at Laboratorios Almirall S.A.
Peter Allen	Finance Director	Did not join Celltech until 1992, when he became the Finance Director.	Chartered Accountant	<i>Group Financial</i> controller of Associated British Ports Holdings PLC & L'Oreal UK. Marketing executive at International Management Group. Articles at KPMG Peat Marwick.
Dr. Ursula Ney	Director of Development	Project Manager, including briefly the precursor to CDP 571	PhD in Pharmacology from Royal Free Medical College. MBA from Middlesex Business School.	Head of research lab in Switzerland. Roche UK as an inflammation researcher. Joined Celltech in 1988 as a Project Manager.
Dr. Geoff Yarranton	Director of Research	Director of Molecular Biology.	PhD from the Mill Hill National Institute for Medical research. Researcher at Mill Hill.	Joined Celltech in 1982 as a research scientist.

TABLE THREE: OVERVIEW OF CELLTECH'S PRINCIPAL PUBLICLY QUOTED RESEARCH AND DEVELOPMENT ACTIVITIES

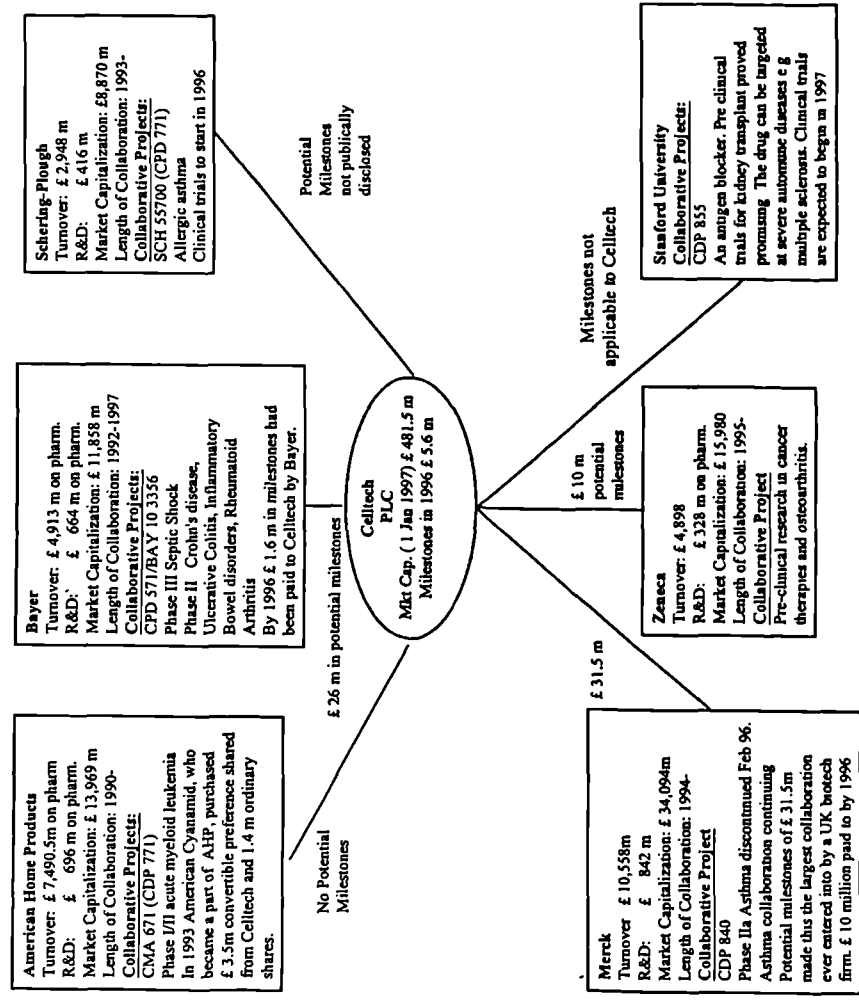
Product Code	Application	Stage of Development	Collaborator
Anti TNF Antibodies CPD 571	Rheumatoid Arthritis	Phase II UK - success	Celltech regained full rights for CDP 571 from Bayer at no cost. New Partners are being sought to work on CDP 571.
	Crohn's Disease	Phase II USA - on-going	
		Phase II UK - success	
	Septic Shock	Phase II US - start 1996	
BAX 1351		Phase III was announced in May 1997 as having failed to show significant efficacy.	Bayer collaboration ends. Bayer paid £15.7 million in milestones. Celltech's own expenditure on this programme was about 15% of Bayer's (around £2.35 million).
Cancer			
CDP 771(CMA 676)	Acute myeloid leukaemia	Positive initial clinical results. AHP commence Phase II/III US trials. European trials expected soon.	American Home Products
CDP 671 (CMB401)	Ovarian	Phase I/II UK trial - results due in 1997.	
Asthma	Lung	Phase I/II expected to conclude in 1998.	American Home Products
Phosphodiesterase Type IV inhibitors	Mild/moderate asthma	Discontinued trials due to unfavourable results. Collaboration continues to follow other leads.	Merck
SCH 57000 (CDP835)	Asthma	First European trial expected during 1997.	Schering-Plough
Gene & Drug Targeting CDP 850	Inflammation	Phase I/II trial on psoriasis in UK on-going.	
Selective Immunosuppression CDP 855	Blood antigen presentation	Pre-clinical trials in kidney transplantation. Will target at severe autoimmune diseases e.g. multiple sclerosis	Stanford University - Strong patent position being established
Inhibitors ZAP70	Immuno-suppression	Pre-clinical identification of potential development compounds	
Metalloproteinase Inhibitors	Cancer	Pre-clinical. 3 novel enzymes identified. Patents filed	Zeneca
	Osteoarthritis		

TABLE FOUR: OVERVIEW OF SEVEN LEADING UK BIOTECH FIRMS

Company Name	Market Capitalisation ⁵⁴ & equity raised	Cash Reserves (millions)	R&D Spending (millions)	Staff	Major Areas of Interest	Rough Stages of Clinical Development (publicly reported)	Collaborative Partners (excluding universities)
Celltech	£ 214.7 (£112 equity & £50 asset sales raised)	£ 46.4	£ 17.4 (1996)	200 +	Cancer, Inflammation, immunomodulation	5 clinical trials on-going (1 at phase II/III) 4 pre-clinical studies	American Home Products, Bayer, Merck, Schering-Plough, Zeneca.
British Biotech	£ 1,001.8 (£389.5 raised)	£ 213.1 (after share issue)	£ 29.1 (1996)	292	Cancer, Inflammation, Virology	16 clinical trials across 6 products (2 at phase III). 3 pre-clinical trials.	Glaxo-Wellcome, InSite Vision, Immunotech, SmithKline Beecham.
Cantab	£112.2 (£159.5)	£ 39.6 (interim July 1996)	£ 6.3 (1996)	91	Cancer, Inflammation, Infectious Disease via immunotherapeutic vaccines	2 clinical trials at phase II, 1 at phase I, with more in the pre-clinical pipeline	Glaxo-Wellcome, Pfizer, SmithKline Beecham.
Chiroscience	£ 246.2 (£ 91.6 since 1994)	£ 47.7 (interim June 1996)	£ 12.1 (1996)	166	Chiral compounds (R&D includes RNA virus infections e.g. Hepatitis C, Cancer, local anaesthetic)	1 product on the market, 2 clinical trials at phase III, 2 at phase II, and 1 at phase I. 12 candidates in development	Chungai Boyeki, Conti BPC, Knoll (sub of BASF), Laboratorios Menarini, Medeva.
Peptide Therapeutics	£ 108.3 (£36.5)	£ 23.6 (1996)	£ 2.1 (1995)	64	Allergy, Rheumatoid Arthritis	1 clinical trial at phase II and another product at phase I.	Alizyme, Biomire (Canada), Dr Fooker Laborien GmbH (Germany), Medeva, Mochida Pharmaceuticals (Japan).
Proteus	£ 23.9 (£ 37)	£ 15.8 (after £13.5 post account share issue)	£ 5.5 (1996)	65	Immunotherapeutics (control of sex hormone dependent tumours), DNA binding, Enzyme Inhibitors (HIV, Blood Clotting), Inflammation (arthritis), BSC test	1 phase II trial being conducted by a collaborator 1 future BSC testing product	Enfer Science, Janssen Pharmaceutia, M.L. Laboratories.
Scotia Holdings	£ 223.4 (83.8)	£43.5	£ 16 (1995)	340	Lipid Technology, Cancer, Dyslexia	At least 3 products on the market 6 clinical trials (1 at phase III) 16 pre clinical candidates	Astra pain Control (Sweden). Distribution agreements with: Abdi Ibrahim, Beiersdorf (Nivea), Galderma (L'Oreal/Nestl), G.D. Searle, Whitehall Italia Spa.
Total	£ 2,104.2 (cap)	£ 433.2	£ 88.5	1,218			

⁵⁴ Market Capitalisation in millions of pounds as at 1 August 1997

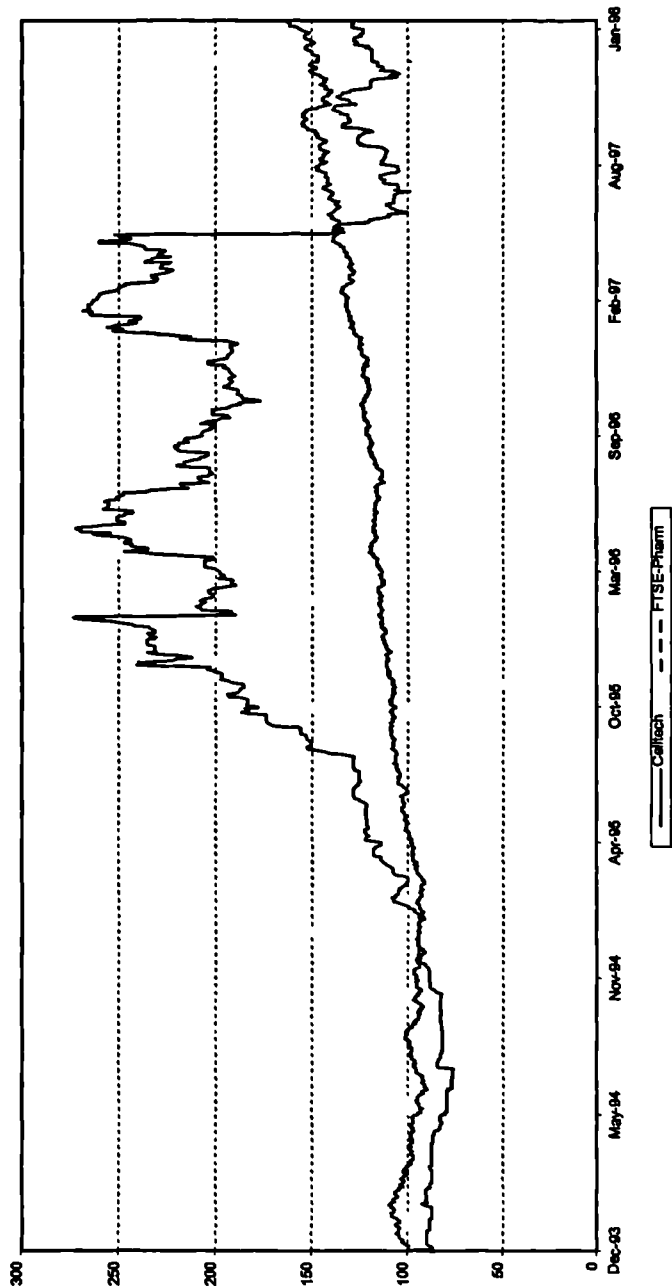
FIGURE ONE: CELLTECH'S NETWORK OF MAJOR COLLABORATORS



(Total Potential milestones from all collaborators = £ 83 m)

Sources of Information: Company Reports & Web Sites, Fortune May 15 1995; Financial Times, Market Guide Web Site.

FIGURE TWO: PERFORMANCE OF CELLTECH VERSUS FTSE PHARMACEUTICALS MARKET INDEX



Celltech share price and FTSE Pharm Index both indexed at 100 on December 8 1993.

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Appendix Two

THE POLYMASC CASE STUDY:

Formation, flotation and early years of a new quoted UK biotechnology firm

INSTITUTIONAL AND TECHNOLOGICAL HERITAGE

The Royal Free Hospital School of Medicine, University of London

The origins of the company are to be found in a challenge to the School of Medicine in the 1980s in which it was argued that the departmental structure was inappropriate for the advancement of clinical solutions to medicinal problems. In response to the challenge the university set up a multi-disciplinary unit known as the Molecular Cell Pathology Laboratory (MCPL). The MCPL combined the capabilities of the Royal Free's Haematology and Biochemistry departments. As Dr. Gillian Francis, the current Chief Executive of PolyMASC and the then head of the MCPL, recalls the purpose of the unit was 'translating what you know at the molecular level through to a cell biological level into pathology and hence into medicine'

Reflecting back on the origins of the MCPL she noted that:

"The history of the Molecular Cell Pathology Laboratory is itself quite interesting. It is actually based upon a critique which was given to the medical school about the problems of generating real life solutions to clinical problems when we were working within the traditional university structure. Our criticism was that the departmental structure was acting as a disincentive to real-life research. Fine for academic problems and model systems, but not fine for getting things through to the bedside because you had all the biochemists in one department, the haematologists in another, pharmacologists in another, and so on. {The setting up of the MCPL}⁵⁵ has been a very powerful move."

⁵⁵ Items in {} brackets are interpretations of what the interviewee was referring to in the relevant quote.

This group began to make considerable progress during the 1980s. By 1988 MCPL had filed three patents. The group was beginning to move from blue skies research and closer towards the stage of translating its research into real products which needed to be tested in the clinic. The Royal Free had engaged in considerable drug discovery, but if products were to be developed then a commercial vehicle with which to make substantial financial investments needed to be created. As Dr. Francis puts it:

“The intellectual property which the team had developed was spawning products which were nearing the clinic and obviously as we neared the clinic the costs were escalating. It got to the point whereby it was inappropriate for the university to incur the high level of costs required, so we decided to set up a company and did this by the unusual expedient of floating under AIM” (the London Stock Exchange’s Alternative Investment Market).

Today PolyMASC is still located next to buildings of the Royal Free Hospital. The Royal Free remains a substantial shareholder in the firm. Three of the staff are on secondment from the Royal Free. The intellectual property created by the MCPL was transferred to PolyMASC and the two still work closely together. Clearly much of what PolyMASC is today lies in the roots of the Royal Free.

PolyMASC’s Team, Technology and Thence its Name

Perhaps the greatest legacy that PolyMASC received from the Royal Free was the technology transferred to it upon its creation. This technology is embedded in explicit patents and more tacitly through the staff who invented them and were transferred to PolyMASC. The relationship between the newly created PolyMASC and the Royal Free was summarised by the company’s placement document in 1995 as follows:

“proceeds of the Placement will, inter alia, be used to acquire, from RFHSM {Royal Free}, the necessary intellectual property (which will include an assignment of the existing patents and patent application) RFHSM, has conditionally subscribed at par for Ordinary Shares and, following the placing, will hold Ordinary Shares representing 26 per cent of the enlarged share capital

of the Company. RFHSM has contracted with the Company in relation to the provision of certain services for at least five years and to second certain key members of staff to the company as required.”

The Founding Scientists

The core scientific team which PolyMASC assembled upon its creation was seconded from the Royal Free. This team had a deep tacit knowledge of PolyMASC’s key technology, as expressed in the patents which they had invented. The team had a history of working together in the MCPL from which they may well have shared common experiences and views of the world, leading to a shared organisational culture with which they infused PolyMASC. Their deep knowledge of and commitment to these patents made them well placed to translate the knowledge embedded in these patents into marketable drugs. As Dr. Francis put it:

“The motivation for the founding science team was very clear. We made this. We’ve spend a tremendous amount of our academic life creating this stuff and it would be a tremendous disaster for us not to see it through into the clinic, not to have it survive, because good technologies can fail for human reasons rather than because of flaws in the technology.”

Leading this group of scientists is Dr. Gillian Francis. She is listed as the principal inventor of five of PolyMASC’s patents and co-inventor of a sixth. She has twenty one years experience in research of growth factors and cytokines, a key aspect of PolyMASC’s research, and ten years experience in PEGylation⁵⁶ of proteins. Dr. Derek Fisher, the former Deputy Head of the MCPL, moved to PolyMASC as the Director of Biochemistry. He is also a sole inventor of one of the company’s patents. He has twenty one years experience in polymer science, and ten years experience in PEGylation. Dr. Christina Delgado, the Director of Pharmacological Research of

⁵⁶ **PEGylation** involves the attachment of a synthetic polymer polyethylene glycol to biological molecules. The purpose of PEGylation is to reduce harmful reactions by the body’s defences to some therapeutic drugs and to make longer lasting agents by reducing removal from the body and/or destruction of the agent.

PolyMASC, was the principal inventor of one of the MCPL's patents and the co-inventor of another. She has thirteen years experience in polymer science and ten years experience in PEGylation. Clearly the three principal founding scientists have considerable research experience in the key technological areas in which PolyMASC is involved, namely polymer science, PEGylation of proteins, growth factors and cytokines. Other personnel transferred from Royal Free include Dr. Farooq Malik, who specialises in PEG-cytokines and is listed in the 1995 Prospectus as one of the joint inventors of one of PolyMASC's Polymer Modification patents; Dr. Ajay Agrawal, who specialises in liposomes⁵⁷, a key technology in which PolyMASC is involved; and Josephine Kandler the laboratory manager, who has over 20 years experience in biomedical research.

The Technology

Molecular Altering Structural Chemistry is a set of techniques for attaching polymers to molecules. At the moment the preferred polymer which PolyMASC is employing is PEG (polyethylene glycol). This is not a new technology. PEG was discovered about thirty years ago. There are currently 2 products on the market, with several more in clinical trials. These products, ADAGEN (to treat the rare condition commonly known as the 'Bubble Boy Disease') and ONCASPAR (to treat acute lymphoblastic leukaemia), developed by Enzon Inc. of the USA, were approved by the FDA in 1990 and 1996 respectively. The first patent family in this technology, developed by Enzon

⁵⁷ A liposome is defined as "a small capsule made of lipids. Lipids can form stable sheets of molecules in solution, in which the polar 'heads' point outwards into the watery solution and the apolar 'tails' stick together in the middle of the sheet. If such a film closes up into a ball, the result is a sphere with watery solution outside and inside separated by a lipid 'bilayer'. This is a liposome."

"Liposomes have been suggested as the basis of several methods of drug delivery, especially for the delivery of peptide drugs. This is because they could protect their contents from digestion in the stomach and so deliver them to the intestine, where they would be absorbed, or could allow them to be injected into the bloodstream and be carried around to a specific organ"

Source: William Bains (1995) *Biotechnology from A to Z*. Oxford University Press.

Inc., expired in 1996⁵⁸. The principal area in which PolyMASC is involved is in PEGylation of protein and peptide (protein fragments) pharmaceuticals. The discovery of cytokines, which are proteins that send messages to the body's cells, offers potential for new pharmaceuticals, however they are not without their problems. According to PolyMASC, the principal problems are that large proteins are not removed by the body's defences within hours, while peptides are removed within minutes by the kidneys, many foreign proteins can trigger life threatening immune reactions, many are also insoluble in water making them difficult to inject, and finally up to 80% of the injection can be wasted, thus increasing the cost of the dosage (Web-site and interviews).

One solution to these problems, offered by the promise of biotechnology, is recombinant technology whereby many of a drug's foreign features are removed so as to reduce the potential of an immune reaction. However, many of the problems remain and another solution is PEGylation. As Dr. Francis puts it:

“Cytokines form the basis for making many excellent therapeutics. However they are not very good pharmaceuticals. The attachment of the polymer solves many of the problems of converting these molecules into pharmaceuticals”

PEGylation is basically a concealment technology which fools the body into thinking that the protein, or peptide is water and hence does not trigger an immune response. Dr. Stephen Charles, PolyMASC's Commercial Development Director, notes that the essential characteristics of the PEG polymer are that it is very mobile, covered in water and consists of long linear chains. As he put it:

“Those characteristics tend to make this look like water. So if you are another molecule coming along to have a look at this, or a cell based system to clear it and get rid of it, then all you see is water. That's the trick. So it is a concealment technology. It's a man made mask as it were.”

⁵⁸ Details regarding Enzon Inc. are from the company's web site <http://www.enxon.com>

It is on this concept that the name of the company is based. Poly stands for polymer, while MASC stands for Molecular Altering Structural Chemistry. MASC can also be interpreted as a means of hiding something, or a concealment technology. Hence PolyMASC is essentially a company which seeks to offer medicine a concealment in the war against disease.

The PolyMASC PEGylation is considered by the management to be superior to those currently on the market. Other techniques on the market employ relatively harsh chemistries, which can damage the protein to which the PEG is being attached. The advantage of the PolyMASC PEG is that it can be applied under relatively mild, physiological, conditions. Another advantage of the PolyMASC PEG, according to its web-site, is “that the reaction mixture is relatively innocuous and does not have to be removed before the PEG protein is exposed to the target cells in many assay systems.” The management believe that these advantages will enable PolyMASC to be successful in attracting custom to its PEG technique over rival products on the market.

To move from concept, as expressed by patents, through to actual drugs delivered to the bedside it was necessary to create a commercial infrastructure through which the creative energies of the founding scientists could be translated into products. The remainder of this case study relates the story of how this team sought to create and develop this commercial infrastructure.

THE AIM FLOTATION

Context in which the Firm was floated

The first step in the creation of this commercial infrastructure was the establishment of a company independent of the university structure. The university would have found it difficult to justify the considerable financial investment in the risky enterprise of bringing drugs to the market, rather than fundamental research which is a core function of a university. Furthermore, the culture and organisational structure necessary to bring PEG to the market differed radically from that of the university. Dr. Francis sums up the options which faced the founding scientists in 1995 as follows:

“It became very clear to everybody that we had two options:

1. We could have licensed all the technology to an individual pharmaceutical company as an academic unit, and then it would have gone into a handful of products, because that’s all that a pharmaceuticals company could add that was applicable, it would be all that they could get through in the time before the patents expired.

It was a decision we all took at this time that if we wanted to get a lot of this technology through to many pharmaceuticals, the only way to go was

- 2 the second way, to set up a company and license the technology on a product by product basis.”

The founding scientists were successful academics. Without the entrepreneurship of these scientists PolyMASC would not have been created for it was through the leadership of Gillian Francis that the MCPL was created within the ‘Royal Free, combined they had created the core patents, and it was they who led the group out of the university structure and into a public company. A key question then is why did they do so? The answer is that they wanted to remain a part of the process, to shepherd their technology through initial discovery to market application. Dr. Francis captures the essence of this motivation as follows:

“the core science team are the scientists who have built their knowledge base and their remit as academics is to get it through to the bedside ... I guess a lot of us feel that we are on a sort of mission, a crusade.”

PolyMASC was the first biotechnology firm in the UK to move directly from the university structure to a listing on the stock exchange (Annual Report 1996). AIM is a market set up by the London Stock Exchange to enable young companies with high growth prospects to raise share capital. The rules of this market are less onerous than the Official Exchange and is often viewed as the London’s rival to New York’s NASDAQ. It should be noted from the outset that PolyMASC was viewed by AIM as an exciting high technology firm with strong growth potential and an entrepreneurial

management team. This is reflected in the fact that PolyMASC's CEO, Dr. Francis, was awarded the Entrepreneur of the Year Award by AIM in 1996.

Creation of a biotechnology firm here in the UK has been eased by increasing awareness of the growth potential of the sector and changes in stock exchange regulations. Sir Brian Richards, one of the founding fathers of the UK biotechnology sector, recently noted that access to venture capital for biotechnology firms has become easier in the mid 1990's (public lecture at City University, February 1998). In 1990 there were no biotechnology firms listed on the London Stock Exchange due to rules of the exchange which required all firms entering the market to have an established profitable track record. Without access to a public listing the opportunities for Venture Capitalists to realise a capital gain on their initial investment were limited in the medium term. Shares could only be sold by the mechanism of matched trading and this is not a practical option for a large investor. Access to a stock exchange listing was made possible by changes in the rules of the exchange in the early 1990s (pioneered by British Biotechnology and Sir Richards). With a listing the liquidity of a company's stock rises hence offering Venture Capitalists an opportunity to exit their investment once a capital gain has occurred.

Since the early 1990s there has been a rush of biotechnology firms listing on both the Official Listing and AIM. By the time PolyMASC sought flotation the market had established an understanding of the sector and was more open to investment in the sector. Solid technological basis and a strong management team are still required, however there are now a growing number of investors familiar with the sector. Thus when PolyMASC launched itself on the market in 1995 it was not in totally uncharted waters from the perspective of the investor.

Impact of the AIM Listing

The AIM listing had the dual effect of raising much needed share capital and subjecting the firm to the rigours of regulation by both AIM and institutional shareholder monitoring. An AIM listing also offers the firm the option to return to the

market for fresh capital, subject to its performance, nor does this listing preclude the firm from seeking a London Stock Exchange Official Listing in the future.

The firm employed Teather and Greenwood to manage the placement of five million shares at a price of £1 per share in December 1995. The placement was over subscribed. This issue, combined with issues of a small number shares in August and November, raised £4.5 million after £633,000 in expenses (Annual Report 1996).

The company's shares traded strongly in its early days. By the end of January 1996 the price had risen to £1.57, increasing the firm's market capitalisation from the placement value of £20 million to £31.4 million. Just prior to the firm's second AGM in March 1998 the price of the shares had stabilised around £1.175, or a market capitalisation of £23.5 million. Table One outlines the principal shareholders as at March 1998 versus the minimum amounts to be held by associates of PolyMASC and the Royal Free on flotation.

INSERT TABLE ONE ABOUT HERE

Just after the placement in 1995 the major shareholders were the founding scientists, with a combined 31.75% share of the company, and the investment arm of the Royal Free (Freemedic) with 26%⁵⁹, Medical Marketing International had a 5% holding, with an employees' share option trust (PolyMASC ESOP) and other directors controlling a further 8.93% of the company's shares (Placement Prospectus). With the exception of the holdings of the Royal Free, which have declined by around 13%, this position remains largely unchanged in 1998 indicating the continued strong ties between PolyMASC as a corporate entity and its institutional heritage from the Royal Free. From Table One it can be seen that Royal Free, the founding scientists and the directors retain a majority shareholding (50.39%), with a further 6.25% held by PolyMASC ESOP. Thus while the City of London, through institutional and private

⁵⁹ It is worthy of note that the transfer of intellectual property rights and tangible assets from the Royal Free to PolyMASC at its foundation involved the transfer of 5.2 million shares to the Royal Free at a price per share of .1 pence each, or a total of £ 5,200. The value of this holding at the day of the placement was £5.2 million and as at March 1998 it would be worth £6.12 million.

shareholders, does exercise influence over the company, it is a minority interest. The market discipline imposed on this company by the stock market may be lower than other biotechnology companies (e.g. Celltech or British Biotechnology) where the founders and employees have a clear minority interest in the firm.

POLYMASC'S STRATEGY

Having outlined the company's institutional heritage and the AIM listing this case now turns to a direct Exploration of the strategy which underpins the success of PolyMASC to date. The reader's attention is first directed towards the technological strategy of the firm and then its commercial strategy, separating out its strategic and financial goals.

Technological

The underlying technological strategy of PolyMASC is the development and Exploitation of a platform technology, namely PEGylation. PEGylation is believed by the firm to have a wide number of applications. As Dr. Charles puts it:

“PolyMASC is different because we add value to other people's drugs. We can take an existing protein based pharmaceutical product, something that is currently on the market and improve its performance considerably by attaching one of our polymers ... We do not just attach PEG, the polymer, to proteins and peptides, we can attach it to liposomal delivery systems ... We have PEGylated living cells. We have PEGylated viruses. We have PEGylated red blood cells. We can PEGylate anything that moves. So what that means is that there is an incredibly broad range of opportunities.”

Another advantage of this kind of platform technology is that for a young company like PolyMASC it may well be able to get drugs to the market quickly by piggybacking on an already approved drug. Thus the firm can get a drug to market much quicker than the decade or longer that it often takes to steer a new and novel chemical entity through the regulatory process. As the 1996 Annual Report notes:

“Our advisors on regulatory procedures have confirmed the view of the Directors, expressed at flotation, that the time to obtain regulatory approval of a

PEG-modified variant of a clinically established protein or peptide pharmaceutical will be substantially less than the equivalent initial approval.”

As previously mentioned this platform technology is not new, therefore to be successful in a crowded patent market PolyMASC’s technology needs to be clearly superior to rival techniques. PolyMASC appears to have a real advantage here. The Prospectus states that there was only one company (Enzon Inc.) specialising in the delivery of PEGylated techniques to pharmaceutical firms. As stated earlier, the initial patents surrounding Enzon’s technology were due to expire in 1996, though according to Enzon it has developed second generation PEG patents⁶⁰. The view of PolyMASC’s management team, as outlined earlier, is that their technology offers clear advantages over current patents, is supported by the Expert’s Report in the Prospectus which states:

“On the basis of initial data we believe that the PolyMASC chemistry can indeed show advantages over competing technologies particularly in the modification of labile proteins and PEG-liposomes”

Building Patent Protection

Having a superior technology was not sufficient to realise the potential of a platform technology. It was essential for PolyMASC to legally protect its core technology via patents. The Expert’s Report in PolyMASC’s Prospectus states that:

“It is clear in such a competitive field, which has many issued patents, a well formulated patent strategy for generating and protecting new intellectual property is of prime importance”

The management of PolyMASC sought to address this issue squarely at the foundation of the firm. Four patent families were transferred from the Royal Free to PolyMASC and the four inventors, or co-inventors, of the relevant patents were seconded to, or employed by, PolyMASC. The firm sought to further lock in these key personnel by ensuring that they were major shareholders as outlined in Table One. All these

⁶⁰ Enzon web site <http://www.enzon.com>

scientific staff were precluded, under AIM rules, from liquidating their shares for the first year of trading. In the first two years of trading PolyMASC has not only employed external agencies to advise on its patent strategy but has successfully defended an opposition against one of the patents in its four active patent families (PEG-liposomes). It has built on its initial patent families by making new patent applications (in gene therapy and cancer with its partner Genzyme and in an additional polymer conjugates technique) and has also entered into partnerships to generate additional future patent applications (for example in the area of human growth factors via a collaboration with Oxford Molecular). An overview of the management developments in PolyMASC's patent portfolio is contained in Table Two.

INSERT TABLE TWO ABOUT HERE

COMMERCIAL

Strategic Goals

The long term goal of PolyMASC is not to become a fully integrated pharmaceutical firm, rather it will focus on licensing out its PEGylation technologies, the development of promising new chemical entities up to the early stages of regulatory development, and the extension of its PEGylation platform technology. For PolyMASC the fact that its strategy is centred around a platform technology, which has a wide variety of applications, is a decided advantage over other biotechnology firms who have invested the majority of shareholder's funds in the clinical discovery and development which seek to address the needs of a narrow range of illnesses. As Dr. Charles puts it:

“One of the good things about PolyMASC is that it has a platform technology. Unlike most biotech companies, where they have one or two wonder drugs, which, if they fail that's the end”

The other side of this approach is that the company has a lower upside potential. If a wonder drug does make it through to market then sales can be several hundred million dollars per year. Thus while the platform technology strategy reduces risk, it also reduces shareholder returns. To add some extra 'spice' for PolyMASC's shareholders the firm has broadened its strategy to encompass a limited amount of investment in

collaborative and independent drug discoveries. Should these projects succeed the firm will have a greater percentage of royalties on the final drugs than if it licensed out a PEG product to a company which is then attached to one of its current drugs. Reflecting back on this evolution in commercial strategy Dr. Charles recalls that:

“When I joined the company {in October 1996} plans to have our own development work was not yet implemented. It was initially a pure licensing strategy. In other words here’s PEG, lets go and find the big players and PEGylate their products and the money we make from doing that will make PolyMASC profitable and that is true ... Now we are pursuing these three opportunities {which are the aforementioned alliances with Oxford Molecular, NOF and Hydro Med Sciences} which we feel would benefit our shareholders considerably, because it would give us the opportunity to license the product much further down the cycle”

Thus the strategy of the firm has broadened from contracts focused on licensing out of technology to a more balanced portfolio of contracts:

- Out-licensing of technology for third party products
- Strategic Partnerships with shared development and profitability
- Sole development to clinical trials to add greater value with subsequent licensing (PolyMASC Web-site)

Dr. Charles sums up the core commercial strategic direction of the firm as follows:

“We do not intend to become a Vertically Integrated firm ... The initial Business Strategy of the firm is to form collaborations with a variety of large and small pharmaceutical companies, who have on the one hand existing products on the market, or new products in development, all of which could benefit from PEGylation, or polymer attachments, and then strike up deals with each of these companies. So we will have a broad base so that if one or two fall out we will still have a viable business, rather than having everything hinge on one or two clinical trials ...”

Financial Goals

In the short term the principal financial goal of PolyMASC, in contrast to that of most other biotech start-up firms, was to conserve its scarce cash resources. PolyMASC has sought to achieve this goal by breaking even within the first two and a half years of its foundation. November 1997 was a landmark as it was the first month in which the firm's income exceeded expenditure. The management are seeking to break-even in the medium term, and perhaps even make a profit, through its licensing business, while in the longer term profitability can be boosted by royalties from drugs which are licensed out to companies for use in successful drugs. This, according to the firm's Prospectus, would take a minimum of five years after a licensing agreement was signed, as the drug would have to go through regulatory approval before going on the market and thus activating sales based royalties.

Dr. Charles sums up the financial strategy as follows:

“The underlying licensing business which PolyMASC has will break-even and return profitability in the short term ... Clearly the later, or the further down the development path you can take a drug before you license it the larger and higher the royalty income. We will probably never directly market anything. So we are dependent for our big income, our real income, on royalties from our marketing partners. We want to get these numbers as big as possible {hence the firm would like to take drugs as far down the development process as its current resources and capabilities enable it to} What we are aiming to do in our research programs is to cover the costs of the scientists and running the company. Any license fees and royalties would take us into profitability.”

Table Three summarises key elements of the financial performance of PolyMASC since its formation. From this table we can see that cost of sales as a percentage of turnover has greatly declined from 317% to 125%. Interest income has declined as the company's capital expenditure and losses have cut into the £4.5 million pounds raised from its AIM floatation. The firm's financial goal of break-even is a practical one. Given PolyMASC's cash burn it will have to return to the capital markets if it does not

break-even within the next few years. Based on an analysis of the financial accounts of several biotechnology firms listed on the Official London Stock Exchange Listing one can see that recourse to bank debt, other than an overdraft, is unlikely to be an option. None of these firms have significant bank debt and many have a history of returning to the capital markets when their cash reserves become low.

INSERT TABLE THREE ABOUT HERE

ORGANISATIONAL DESIGN

Multi-Disciplinary Teams and Meritocracy

Molecular Altering Structural Chemistries (MASC) are being researched by other firms and universities, therefore PolyMASC competes in a real sense with these organisations not only for space in the commercial marketplace but also for scientific talent. To be successful PolyMASC needs to attract scientific talent and use it effectively. To this end the firm has created a culture which it feels is more appropriate for the efficient discovery and commercialisation of polymer attachment technology than its rivals in the universities and pharmaceutical firms.

PolyMASC saw an opportunity to build superior polymer attachment techniques by combining people from different disciplines into the one team. Essentially it sought to combine the abilities of chemists in the building of molecules with the understanding that biologists have about how the body fights disease. Dr. Francis believes that other organisations still have not learned the value of, or lack the ability to, combine these disciplines within one structure. She notes:

“Polymer coupling systems were being built by chemists, not biologists at that time {when PolyMASC was founded}. This is very important. The tendency of the university structure to compartmentalise people, means that people are working with only part of the story ... We thought the major barriers were going to be in academia because of the departmental structure ... but in fact we found it is just as bad in the pharmaceutical industry because it actively adopts extraordinarily linear structures of line managers. Manager A reports to B, C reports to B and thence to A, etc. Those structures being very vertical are also

disincentives to the process {of developing new polymer attachment techniques and applications} ... We have insisted on extremely rigorously destroying any form of hierarchy when we are in the process.

Our strength is in the way we've grappled with the problem - we have not had people working with only part of the story. The saga is quite interesting, because it is still going on. Chemists are still making these polymer coupling systems and expecting them to work. ... {bringing together and} managing a multidisciplinary team, with all the relevant skills from medicine, chemistry through to molecular biology and so on, has been a very fruitful exercise."

As alluded to in the above quotation this multi-disciplinary concept is further refined by what Dr. Francis refers to as the 'suspension of hierarchical processes' during the creation of new polymer attachment techniques, or the attachment of polymers to specific client drug molecules. This suspension of hierarchy involves the creation of a meritocracy in scientific debate. The ideas of all team members, irrespective of seniority, are subject to a process of internal review. Debate is focused on data rather than personality. In the view of senior management this suspension of hierarchy is a critical element of PolyMASC's future success. Commenting on this system Dr. Francis stated:

"When we are working in this process the hierarchy is temporarily suspended. This means that the mechanism is in place for whoever is right to prevail, not whoever is senior. That is something you actually have to work at extremely hard to achieve. People have to suspend a lot of their emotions, their need to dominate, their need or liking for little bits of power, and so on. It's a very difficult thing, we found, to get people to suspend that ... It is an unusual quality {to be able to tolerate suspension of hierarchy} ... Getting people from senior positions to allow the juniors in the team to say no, that's not correct, that's flaky and to allow them to prevail is not always easy for senior people to do. Our success, I am absolutely certain, relies on the fact that we have been able to suspend that hierarchical process."

'Ideas Merchants' and 'Human Databases'

One of the interesting aspects of PolyMASC is how this meritocracy challenges the core of one's personal beliefs on the value of their ideas. Scientific discovery is based on the re-conceptualisation of the world, the generation of new ideas by individuals and teams. It is a natural tendency for people to feel that theirs is the important idea, the break-through. Not so in PolyMASC. Dr. Francis distinguishes between what she refers to as 'ideas merchants' and 'human data bases'. At the heart of PolyMASC is the linkage between these two kinds of people. Combined they have a powerful role to play in the creation and application of new ideas, alone they can achieve little. The managerial problem is that no one likes to be viewed as a 'human data base', everyone wants to be thought of as an 'ideas merchant' for they are the people the wider world remembers. Fundamental to getting these people to feel comfortable working together is the suspension of hierarchy. Dr. Francis summarises the creative and managerial relationship between 'ideas merchants' and 'human databases' as follows:

“Because we can suspend that process it allows the ideas merchants in the team to access the human data bases. Now the ideas merchants may not be in possession of all the information. But the human data bases, some of whom rarely have ideas, {are vital to the process} provided that you can somehow make them emotionally comfortable with the position of being not on the whole an ideas merchant, it works well. That is a difficult trick to pull because there is so much cachet in society for the ideas merchant that we've found that quite a lot of people can suffer a lot of emotional stress at finding that they are unable to be an ideas merchant and finding that they are being slotted into the {role of a} human data base. We have to address the emotional needs of these individuals, because we are doing things that act across people's emotional needs, part of the thing about this process of suspending hierarchy is that it is temporary.

This happens when we meet together to do science. When we stop doing science and go off to the pub, all the normal things like fighting to win an argument and having your vanity can all be there. At a cocktail party argument fine, that stuff's appropriate. But it isn't appropriate for argument which is in

effect discourse to dissect the truth, people have to be willing and able to suspend all that normal emotion. We're quite open about all this. We tell people when they join, for heaven's sake, don't fight to win an argument. Defend an idea that you feel must be defended. Convince on data or convince on logic; use your knowledge. The usual kinds of shifting sands argument, that has to be seen for what it is and weeded out and this is a hard nosed policy."

It is natural that most of the 'ideas merchants' are likely to be those who founded the company and have crystallised their ideas through many years of academic development and commercially viable patents, however new people do serve an important role in the firm as catalysts and key sources of knowledge. The challenge is to successfully interface idea with the rich data and knowledge that 'human databases' offer. Dr. Francis alludes to challenges of this relationship when she comments that:

"New people bring new and larger data bases and I am sure that some of them will also bring new and fresh ideas. It depends what your threshold is for dignifying something with the notion of idea. But certainly the new people are making an input. I think there is a culture shock for people coming from large teams, because large teams, or teams that don't work as we do, don't accustom them to what is a very heavy amount of peer scrutiny. I mean even though I am the founding scientist of the company, if I write a document I submit it for peer scrutiny and it gets kicked around. Anything that's produced gets kicked around. And basically, if it has a flaw you just have to take it on the chin and be glad it's been improved. We have people who have come in from pharmaceutical companies who think well, I should be in charge of this and that should mean that I am beyond scrutiny. We have no-one beyond scrutiny, certainly not at the scientific level. In fact we expect it. It's sort of an internal peer review process ..."

Managing Tension: Motivation and Communication

As can be seen the multi-disciplinary team is not without its challenges. On the one hand it may lead to a technically superior product and attract scientists who enjoy

working in inter-disciplinary teams, on the other hand it represents a direct challenge to the dominant ways of working in more traditional organisations with which PolyMASC competes, namely universities and pharmaceutical firms, and at a deeper level how people view the value of their own ideas. This could lead to considerable conflict as the organisation grows and more people need to be co-opted from traditional firms and into PolyMASC. Dr. Francis is aware of this managerial challenge and observes that:

“I know from past experience that in this culture {where hierarchy is suspended and people who come from traditional hierarchical organisations enter PolyMASC} these people will become disaffected very, very rapidly and this is one cause of staff turnover ... It is a very small team and the impact on the psycho-dynamics of the team from new individuals is actually very profound. You can watch it happen, and this ‘syncytium’⁶¹ use of minds is a delicate process. Some individuals can perturb it tremendously ... My job is to make sure that the process is working as it should and to rapidly solve the problem if a new member throws the delicate system off balance.”

As noted earlier in this case the motivation of the founding scientists is clear. They have personally created the technology upon which PolyMASC is based. They maintain a psychological and fiscal ownership of the intellectual property of the firm. They are motivated by a strong desire to see their technologies translated into real drugs which can be delivered to the patient’s bedside. As the company grows new personnel are needed to sustain growth. This poses a challenge for the founders: how to align the goals and actions of new employees with those of the founders. Dr. Francis poses the problem as follows:

“Our problem with new people coming in is how to incentivise and motivate them. There is a problem in that we’re almost like a parent fighting for the survival of a child, and we are so committed that there is almost a big gulf

⁶¹ Syncytium is defined as a “mass of protoplasm with several nuclei but forming one cell.” From *The Concise Oxford Dictionary*, 7th edition, Oxford University Press.

between the core team and people coming in. Obviously they don't have these long standing ties with the project."

This gulf is partially bridged by hiring promising new people who match the needs of PolyMASC. Ideally one could identify people whose goals are congruent with the vision of PolyMASC and hire only those people, however PolyMASC have found that the interview process is not always an accurate indicator of a person's suitability to work in a meritocracy based on multi-disciplinary teamwork. Reflecting on the accuracy of the interview process as a selector of employees who will respond positively to the PolyMASC way of working Dr. Francis commented that:

"It is impossible, I have found, to assess properly whether someone is like that at interview. I've found a great deal of fault in the interview process."

This problem is thus addressed through a process of introduction to the PolyMASC way of doing research and business. Promising employees are hired and quickly exposed to the values of the firm as expressed via the multi-disciplinary team work environment. Through direct exposure to these working practices there is an opportunity for both sides to evaluate their compatibility. Those who adapt to the system remain, those who do not adapt depart. As Dr. Francis puts it:

"Over the years, we've had people who can tolerate {the suspension of hierarchy and peer scrutiny at PolyMASC}, survive and remain with the team, and people who can't, people we have to either evict, or wait for them to decide that this is not for them and to disappear."

There is still the problem of how to offer incentives to these people such that they will join the firm to become exposed to the ideals of PolyMASC and ensuring that they stay long enough to enable a mutual determination of to whether they can work successfully within the PolyMASC culture. To this end the company employs traditional incentive schemes, mixed with a connection to newcomers' altruistic desire to bring new and improved technologies to the bedside. Commenting on the motivation schemes in place at PolyMASC, Dr. Francis says that:

“the company structure has built in the traditional motivation schemes, for example employee share holding schemes and all these things, so that the motivation of the newcomers will be fiscal rather than this cross between altruism and the desire to protect one’s intellectual offspring, as it were. Obviously a lot of the new people really lock into the altruistic motives ... although there are people who don’t share these motivations and enthusiasms.”

An essential element of successful interdisciplinary teamwork is communication. As Dr. Francis puts it “understanding the workings of a team who aren’t just working in concert, but are forming almost a ‘syncytial’ brain, doing this by melding their skills - that process is poorly understood.” To aid in understanding this process, day to day operations at PolyMASC are often sub-divided into project teams. Project teams are charged with the delivery of specific techniques or products. For example there is a project team working on the creation of new products in blood growth factors in conjunction with Oxford Molecular.

In charge of each team is a project management group. The key role of the project management group is to ensure that the team is well informed and working together, thus leveraging the skills of individual team members to create more in combination than they could individually. This communication aids in both understanding the process and avoiding the dangers of de-motivation that more linear systems can involve where individuals work in a black box and their efforts are combined via a linear hierarchical process. Dr. Charles emphasises the importance of communication in managing projects:

“One of the biggest jobs of the project management group is to disseminate the information so that people understand it. So that each player within the team knows exactly what they are supposed to be doing and when, but also to have an appreciation of the bigger picture so that they know where they fit, because it can be extremely de-motivating if you are in a black box doing something without any idea why you are doing it or what happens if you don’t do it and so on. PolyMASC’s style is to involve everybody in the whole thing so that they

know exactly where they fit and why they are doing it and what is the reason for doing it.”

One of the greatest challenges for PolyMASC in the future may be managing the evolution of this ‘syncytial’ brain over time as the organisation grows. In 1996 the firm had an average number of employees of ten, seven of whom were scientists (Annual Report 1996). As the firm expands it may become more difficult to attract and manage employees who are driven by the same motives as the founders. Equally it may be difficult to maintain the strong levels of communication across the company if it should experience rapid growth in employee numbers. This case will now turn to one of the most exciting elements of the way PolyMASC does business: the management of alliances.

MANAGEMENT OF ALLIANCES

Goal and Form of Alliances

As noted earlier in this case by Dr. Charles, PolyMASC does not want to become a Vertically Integrated pharmaceutical firm, hence it needs to work in cohort with other firms. Through its partners it gains access to key resources, such as finance to cover research and development expenses, capabilities which PolyMASC at present has chosen not to own in-house, such as management of regulatory clinical trials (drug development), and access to a drugs portfolio to which PolyMASC’s polymers can be attached. The expert’s report in the Prospectus commented that the strategy of not becoming a vertically integrated firm but instead to achieve market success through a web of external partners, while not without risks, was the most appropriate strategy.

“PolyMASC’s aim of developing and licensing proprietary technologies to corporate partners, as opposed to becoming a fully integrated pharmaceuticals company, is in our view the most appropriate business strategy to exploit their core competency and to lever specialist external resources in the most effective manner. Experience in working with pharmaceutical companies does, however, caution that unforeseen delays or changes in priorities can occur and that the timings of some of PolyMASC’s development programmes may change. We

note, however, that PolyMASC has been prudent in setting realistic timelines to get to initial clinical trials.” (Expert’s Report, Prospectus)

As noted in the strategy section of this case PolyMASC has a portfolio of three types of contract with external partners. These contracts can be broadly termed alliances. The first form of alliance is **Out-Licensing**. This involves licensing PolyMASC’s technology to an external partner who then applies it to one of their own drug programs. This licensing strategy is expected to enable PolyMASC to break even or become profitable in the short term. The 1996 annual report notes that several of its potential clients have over twenty drugs in their portfolio which could be enhanced by application of PolyMASC’s PEGylation technology. PolyMASC has entered into several out licensing contracts since its formation, principally with Onyx Pharmaceuticals, Cangene and TKT. The second form of alliance which PolyMASC has entered into are **Strategic Alliances** which involve PolyMASC and its external partner sharing the costs of development and a share of the profits if products from the alliance eventually make it to the market. According to Dr. Charles PolyMASC has entered into at least three contracts of this nature, namely with NOF, Hydro Med Sciences and Oxford Molecular. The third form of alliance is one which seeks to purchase in capabilities which PolyMASC does not wish to own in-house, but which are critical to the firm’s long term success. These contracts can be called **Out-Sourcing** alliances. PolyMASC is currently involved in one out-sourcing alliance with Shearwater, who provides PolyMASC with access to manufacturing resources and capabilities. A summary of the alliances which PolyMASC is currently engaged in is provided in Table Four.

INSERT TABLE FOUR ABOUT HERE

Partner Identification and Pursuit

Simplicity, it is often said, is complexity cleverly disguised. So it is with PolyMASC’s identification and pursuit of strategic alliance partners. Vertex Pharmaceuticals was

one of the leading US biotechnology firm of the late 1980s⁶². It pursued its strategic alliance partners with a flurry of Trans-Atlantic, Pacific and Continental travel. Technology and times have moved on since then, not only in the bio-sciences but also in communication. What Vertex sought to achieve via the plane, PolyMASC pursues via database faxing, bio-partnering meetings and its web-site. As Dr. Charles commented:

“I don’t advocate jumping on planes and cold calling companies in the US, Europe and Japan, because I don’t think that that works. It does work to some extent, but you have a less than a one percent hit rate. And it is very expensive and time consuming.”

PolyMASC’s approach is parsimonious. It has, according to the management, yielded considerable commercial success for a firm of its youth. In the first instance this success can be observed in the number of firms which were interested in PolyMASC’s technology. Dr. Francis, in a Press Release dated September 1996, commented that “we have already met with over fifty companies around the world to discuss potential collaborations.” This was reinforced by a statement in the 1996 Annual Report which noted that “the high rate of identification of potential commercial partners almost exceeded our ability to service their interest in Q2/Q3 1996.” To be truly successful, however, it was important that the process of attracting potential partners be both efficient, that is attract the maximum number of partners whose drug portfolio could actually benefit from PolyMASC’s technology, and secondly be effective, that is actually lead to signed contracts. To be both efficient and effective PolyMASC employed a systematic approach to partner identification and negotiation.

Dr. Charles sums up PolyMASC’s approach as follows:

⁶² The story of the first few years of Vertex Pharmaceutical’s corporate life is a fascinating and easy read. The Vertex story is narrated in Werth’s book entitled *The Billion-Dollar Molecule: One Company’s Quest for the Perfect Drug*, published in 1994 by Touchstone of New York.

“Part of the strategy is opportunistic obviously. Some may just come through the door, most of them do, but in terms of finding corporate partners I have three approaches, bio-partnering, database mailing and our web site.”

Bio-partnering meetings are rather like dating clubs for potential pharmaceutical and biotechnology alliance partners. These meetings enable a small biotechnology firm such as PolyMASC to target a broad number of potential partners at one location. More importantly bio-partnering meetings are designed to establish fruitful contact between companies who have common interests, or needs. This is facilitated through a database which the bio-partnering organisers have, listing key details of all attending the meeting, such as what are the key products and services which they offer to, or need from, partners. Dr. Charles describes the bio-partnering process as

“meetings that have been organised to facilitate meeting the right people. They {the conference organisers} have a database of people who are going along and you get that database before you turn up. You select from the database the people who you would like to meet and feed that into the organisers and they set the meetings up for you. {When compared to standard scientific conferences} all your lunches are taken up with meetings, but now they are meetings with people who you want to meet ... It’s great. There is a bio-partnering desk at the meeting and there are one or two people sitting behind it. They can answer queries and track people down. It works a treat ... you meet everybody that you wanted to meet. Fantastic.”

Bio-partnering meetings can generate an enormous number of potential leads. Following-up each one of these contacts in person could be very expensive, given that they originate not only from within the UK but also internationally. Dr. Charles has come up with a very cost effective mechanism of following up these contacts. He has designed a very comprehensive web-site to which all contacts are initially referred. This web-site contains detailed information on PolyMASC’s technology (both for scientists and non-scientists), outlines PolyMASC’s key scientific and administrative staff, provides an overview of the company’s commercial strategy, and includes all the firm’s Press Releases, which provide information on financial results, details of

alliance deals, and progress of the firm's technology. Dr. Charles summarises the interconnection between bio-partnering meetings and the web-site as follows:

"I had been in the company two or three days and we went to one of these Bio-partnering meetings I have told you about and I came out with forty leads. Each one was different. It is just an enormous task overcoming that problem. Just getting back to those people with detailed responses to their questions. So I thought that the best way to do it is to have a Web site. Everything they need to know is on the Web site. The technical section is extreme. It is broken up into bits. There are short summaries at the start and you can go down into more detail. This really took away all of the follow-up. The first stage of follow-up is the Web site."

With the growing usage of the Internet in business life the web-site has become a marketing tool in its own right. According to Dr. Charles an increasing number of people are searching the Internet for polymer attachment services and thus PolyMASC's web-site is beginning to attract potential partners in its own right.

The third approach which PolyMASC employs is database mailing. This involves creating a database of companies which PolyMASC believes could benefit from polymer attachment and then tailoring a fax to the needs of that company and the person to whom the fax is addressed. The success of this method is surprisingly high. The firm has had a response rate of 10% from one of its mailings. The approach is both efficient, being cheap and tailored, and effective, in that one of its current partners, Onyx Pharmaceuticals of the USA, was attracted to PolyMASC via this approach. Dr. Charles summarised the efficiency and effectiveness of this approach when he commented that:

"If you get a 1 or 2% response you are doing extremely well, yet in February we got a 10% response. Two weeks ago we announced the first deal that has come as a result of that mailing ... Database faxing is extremely cost effective. I sit at my desk, either at home or at the office, and I fax these people. As I say we get nearly a 10% response. That's very cheap. And you learn. We are doing it again, but we have modified it slightly. It is very easy to do"

In the past two years PolyMASC's approach to attracting partners has resulted in hundreds of contacts, from which eight active alliances have been signed (as per Table Four). From Table Five it can be seen that PolyMASC has, in pure numbers, compared favourably to some of its more established compatriots on the Official London Stock Exchange. It has established a portfolio of partners on a relatively small budget.

INSERT TABLE FIVE ABOUT HERE

Closing the Deal

The real challenge in developing a portfolio of partners is in successful signing of a partnership agreement and its subsequent management. It is essential that contacts be converted into active partnerships if PolyMASC is to turn its technology into profit. PolyMASC has learned some key lessons from its experience in attracting partners and then closing deals. In his capacity as Commercial Development Director, Dr. Charles highlighted three particularly important aspects in successfully closing a deal, namely, negotiating at the right level inside the other firm, understanding the various stages of the licensing process and negotiating fees based on an explicit project plan.

In establishing a partnership PolyMASC have found it essential that the people with whom they negotiate have sufficient authority to commit their firm to both the financial resources necessary to pay PolyMASC and also the internal resources and capabilities necessary to complete their parts of the project in a timely manner. Dr. Charles states that:

"My goal is to get the right level of people involved so that we can have a meeting that would change the course of the project without having to refer to someone who is outside the meeting. I can see that kind of a problem could occur. The wrong people could be at the meeting. You can spend a lot of time developing the relationship and shaking hands on the deal and all that but, {in the end}, you don't actually get the deal {signed}. So you have to be very careful to make sure that you talk to the right people ...

I develop fairly good relationships with the President, the VP of Business Development and the Research Director during the negotiation of a deal. Usually I get to know the Business Development Director and the Research Director extremely well. During the negotiation, of course, the President has to sign off.”

The level of commitment required by both PolyMASC and, most critically, by its partners varies according to the type of alliance. When dealing with either an out-licensing or strategic alliance contract there are typically three phases, which vary according to the depth of commitment imposed on both partners.

The first phase is a feasibility study. This involves the partner assessing PolyMASC’s technology and services to determine its suitability to the R&D projects in which the partner is currently involved, or how PolyMASC’s technology could enhance the drugs which they currently have on the market. According to PolyMASC’s web-site this phase typically takes nine months. Their goal is to recoup R&D expenses incurred at this stage and convince the partner to enter phase two.

Phase two is when both companies have determined that they can work together for mutual gain. This typically triggers a licensing deal where PolyMASC licenses some of its technology to the partner and works with them to translate the promise of this license into practical clinical trials and thence drugs. This is where the serious negotiation takes place. Dr. Charles notes that:

“When you have done the feasibility study, you get to the licensing trigger. This is where you reach the decision to go {or not}. This decision involves the partner in a lot of expense {namely} launching a project which would lead to a product. {The principal expense which they would incur is that of} going through the various clinical processes. Then they will start to look {more carefully at the deal}. Once you have triggered that, it is a whole different ball game.”

According to PolyMASC's web-site, during this phase the company's main task is the supply of clinical trial materials and the development of techniques for production of the PEGylated protein, peptide, or liposome pharmaceutical. Again, the web-site reports, PolyMASC expects to cover R&D costs during this phase.

Phase three involves a drug actually entering clinical trials. As yet this phase has not occurred in PolyMASC's history. Entry into regulatory clinical trials would trigger milestone payments from the partner to PolyMASC (though in the case of the Oxford Molecular deal it is PolyMASC who pays milestones). As the drug progressed through various stages of clinical trials PolyMASC would receive pre-specified payments from its partner and may be required to provide some data and input into the work of its partner in moving the drug through the clinical trials. Were the drug to enter the market then PolyMASC would obtain some royalties based on sales.

As can see from the above it is the goal of PolyMASC, at a minimum, to recoup its expenses from phases one and two of the licensing process. The key to breaking even is an understanding of what are the costs incurred by each partner. Dr. Charles sums up the method of costing a project and negotiating a fee, as follows:

"The relationship starts with PolyMASC producing a project plan of what is required to PEGylate the client company's protein. It is very nice because you fully cost the project from the bottom. You sit down with the Scientist and figure out who exactly is going to do the work and how much it is going to cost. We come up with a plan which you {the client} can't argue with. One company said to me well OK it takes nine months, it's going to cost £170,000 that's too much and too long. I want it to cost £90,000 in six months. I said well OK you want a six month plan, you want it to cost £90,000, what do you want me to chop off it? Because it won't happen. And that is that. This is a very good negotiating tool to get the price right at the start. You are covering your R&D monies. Part of breaking even, of course, is to make sure the work you are doing for other companies is paid for. That is how you break even."

Operational Management of Alliances

Once a deal has been signed it is essential that the alliance be pro-actively managed. PolyMASC's management style with regard to projects involving external partners is not dissimilar from the management style of internal projects. Again at the heart of PolyMASC's approach is communication within and across teams and use of project management techniques. Dr. Charles explains this communication process as follows:

“Once the deal is signed and they have paid the up-front money and we have started working we put into place three levels of communication. Communication is what it is all about ... One {level of communication} is the chap doing the experiment. He will get to know his, or her counterpart in the other company, so that there is good dialogue between the chaps running around on the ground. Secondly, we appoint a senior scientist as the project manager within PolyMASC. They will have regular contact with the project manager from the other side. Thirdly, I will oversee the whole program from the commercial perspective. I will be free to speak to who ever I like in the other organisation.”

Alliances are micro managed using a project management system. The project is monitored against key milestones. If work is progressing slowly PolyMASC's project management system flags this up and communication is triggered at the appropriate level to determine what is causing the delay and how it should be addressed. Dr. Charles describes the workings of this system as follows:

“What we are trying to do is to put in place communication at all levels in the organisation to flag up issues quickly and nip them in the bud. The Project Plan does that as well. We track it. We have a nice big blue bar which says there is the task. That's how long it is going to take. This is the guy who is going to do it. This is when it is going to finish. It is three weeks long, so here we are today. Within a week we have a black line which the program draws along this blue one and the black one should stop at the end of the blue one and then it starts somewhere else. Of course if the black bar goes past the blue one I can see where it is going and swing it up on the computer. I just look at these things. I am there really to ask the hard question: what's going wrong?”

Once problems have been identified people on the ground devise and enact solutions. As and when necessary these staff can draw upon the advice of the Project Management Group or the more senior 'Science Management Team', in the re-appraisal of the project plan. During this process the alliance partner is kept informed of progress at the appropriate level.

PolyMASC's success is inextricably linked to its alliance partners. As can be seen from above the firm seeks to pro-actively manage the process of identification of partners, the negotiation of partnership contracts and the operational management of projects with external partners. The foundation upon which alliance projects are based is on-going multi-disciplinary work inside PolyMASC to develop and deepen its technical and commercial strategies, as outlined earlier in this case. As PolyMASC is a listed company the ability of the firm to formulate and implement a profitable strategy successfully may be reflected in its share price, therefore this case now turns to a brief overview of the relationship between PolyMASC, its shareholders, and the performance of its stock since flotation.

MANAGING THE PIPER

Why did city shareholders invest £ 5 million pounds at flotation for around a 30% share of the firm? Commenting on the company's first year interim accounts Dr. Francis offered an insight into the motivations of such shareholders observing that:

"PolyMASC's ability to add clinical and commercial value to pharmaceutical products through its enabling technology means that it continues to represent an excellent means of investing in the biotechnology sector without the risk associated with the development of new chemical entities" (PolyMASC website, Press Release)

From this quotation it is clear that PolyMASC was designed as a relatively low risk vehicle for investors to access the potential high capital gains associated with start-up biotechnology firms. During 1996 PolyMASC began to broaden its range of contracts from out-licensing to strategic alliances in which it co-developed drugs. Shareholders

were aware that such a strategic option might be enacted by the management as it was flagged in the flotation Prospectus. Dr. Charles suggests that the relationship between the city and the management is a dynamic one in which they have an oversight role in determining if such strategic alliances will flourish in the future. He observed that:

“The Oxford Molecular, Hydro Med Sciences, and NOF alliances are able to give our shareholders an opportunity to decide to invest more money to enable PolyMASC to take those special cases {strategic alliances as opposed to out-licensing projects} further down the development path to command higher royalties in the end, or they may decide no we don’t want to do that - license it straight away.”

Feedback between the external shareholders and the management occurs through a number of avenues, each of which to some extent can be pro-actively managed by PolyMASC. The principal feedback processes are the Annual General Meeting, analyst meetings, press releases, and share price movements. Dr. Charles, in his capacity as Commercial Development Director, actively monitors PolyMASC’s share price movement and keeps the market informed of developments within the firm. This has a clear effect on the company’s share price, and thence its value. He stated that:

“Our stock is not traded very much, because the institutional investors who are involved with PolyMASC tend to think of us as a higher risk {relative to their non-biotechnology portfolio}. When investing in PolyMASC they purchase a block of shares and they hold onto them. This is good at one level, but it doesn’t do the share price any good because if nothing happens it drifts down, because that is the default setting. It drops. So that is why we live and die on Press Releases. Every time we issued a Press Release this year the share price has jumped.”

Figure One maps the relative performance of PolyMASC’s share price against a basket of all biotechnology companies listed on the Official London Stock Exchange since PolyMASC’s formation in December 1995 up to the end of February 1998. All share prices were indexed at 100 on the first day of trading of PolyMASC’s shares. The basket of shares incorporates one of each of the following shares: British

Biotechnology, Cantab, Celltech, Chiroscience, Cortecs International, ML Labs, Oxford Molecular, Peptide Therapeutics, Proteus International and Scotia Holdings. The basket was calculated using a simple arithmetic mean of the indexed shares. As can be seen from the graph both PolyMASC and the basket have experienced considerable volatility. Both indexes rose during the first five months of 1996, with a decline through to November 1996. The first two months of 1997 led to a considerable capital gain in the basket of shares, while PolyMASC had a more modest gain, which continued into April. Both experienced a sharp decline in their value from April/May up to August 1997, however PolyMASC recovered more strongly and as at February 1998 its relative performance remained above the basket of shares.

INSERT FIGURE ONE HERE

Readers who are interested in mapping the performance of PolyMASC's share price movements against announced events may do so by referring to Table Six, in which these events are listed. Matching Figure One with Table Six lends credence to the assertion of Dr. Charles that PolyMASC's share price can be effected by announcements of events. It is worthy of note that PolyMASC's share price did outperform some individual shares incorporated in the basket. One should, however, compare PolyMASC's performance against this basket with some caution. PolyMASC is listed on AIM, whereas the basket shares are quoted on the Official listing, hence they are likely to be traded more often. Biotechnology firms quoted on the Official listing are also exposed to a considerable amount of reporting in the Financial Times, which may amplify the effect of announcements on their share prices. Additionally several of these firms are quoted in the FTSE mid-250 index, which means that they are subject to automatic inclusion in some institutional investors portfolios. Finally the business which these firms are in varies from that of PolyMASC. Few are following the strategy of developing a platform technology to be applied to another firm's drug portfolio; most are primarily engaged in drug discovery and development.

CONCLUSION

PolyMASC has achieved a lot since it spun out from the Royal Free Medical School in Autumn 1995. It has obtained a listing on AIM, attracted a growing portfolio of

external partners, successfully defended its patents in the European Patent Office, deepened its technological competency, and created a distinct organisational culture and management style. The financial position of the firm is rapidly improving, with break-even achieved in the month of November 1997. Dr. Francis concluded in a recent press announcement that:

“We expect the Company to grow rapidly this year on the foundations laid in the first two years” (PolyMASC Web-site Press Release February 1998).

TABLE ONE: MAJOR SHAREHOLDERS

Shareholder (Ordinary Shares)	Minimum % Shareholding on day of Flotation¹	% Shareholding March 24 1998²
Freemedic (controlled by Royal Free)	26.00	18.48
Dr. Gillian Francis (CEO)	15.10	15.08
Dr. D. Fisher (Director of Biochemistry)	8.20	7.97
Dr. C. Delgado (Director of Pharmacological Research)	6.80	6.46
PolyMASC ESOP (Employee Share Scheme Trust)	6.30	6.25
Bank of Scotland (Stenhouse)	NA	5.55
Bank of Scotland	NA	4.22
Medical Marketing	5.00	3.30
Taylor Young Investment Management	NA	3.10
Other Directors	2.60	2.40
Under Control of Royal Free & PolyMASC Employees/Directors	65.00	56.64
Total	70.00	72.81

¹ Source: PolyMASC Flotation Prospectus

² Source: Hemscott Publishing, <http://www.hemscott.com/equities/company/>

TABLE TWO: OVERVIEW OF A SELECTION OF POLYMASC'S PATENTS

Patent Family	Overview of Progress
PEG Proteins	One patent granted in USA One patent granted by European Patents Office One patent pending in Japan
Liposomes	One patent granted by the European Patent Office and successfully defended in an opposition challenge. Patents pending in the USA and Japan
Polymer Modification	One patent pending in the USA One patent pending under the international Patent Co-Operation Treaty One patent application made in January 1997
<i>Tumor Targeting Liposomes</i>	One patent confirmed by the European Patent Office PolyMASC and partner Genzyme apply for a gene therapy and cancer patent in 1997.

Sources: Prospectus; 1996 Annual Report; PolyMASC Web-site; Extel March 1998.

TABLE THREE: FINANCIAL SUMMARY OF POLYMASC PLC

	1997	1996 (17 months)
	£ '000	£ '000
Turnover ¹	528	117
Cost of Sales ²	(661)	(371)
Gross Loss	(133)	(254)
Administrative Expenses	(981)	(1,020)
Interest Income	139	203
Loss Before Tax	(975)	(1,071)
Fixed Assets:		
Intangible ³	390	520
Tangible ⁴	347	184
Cash at Bank	1,956	2,938
Cash burn years ⁵	1.76 years	2.31 years

¹ All turnover relates to income received from collaborative agreements.

² Cost of sales includes R&D expenses which are fully charged to the P&L account.

³ Intangible assets consist of Intellectual Property Rights, Know-how and Patents. All are charged 20% depreciation per annum.

⁴ Tangible assets consists of Laboratory Equipment, Furniture and Fittings, and Computer Equipment. All are charged 20% depreciation except computers which are charged 33.33%.

⁵ Cash burn is calculated as cash in bank divided by losses before tax. It is a proxy for how long the firm could continue at present levels of income and expenditure without recourse to the capital markets.

Source: PolyMASC Web-site and 1996 Annual Report

TABLE FOUR: POLYMASC'S ALLIANCES

Company Name	Announcement of Alliance	Type of Alliance	Details of Alliance
Cangene (Canada)	Transferred at foundation.	Licensing	PEGylation of Cangene Blood Growth Factors.
Hydro Med Sciences	June 1996	Strategic Alliance	Hydro Med Sciences brings "a hydrogel parental drug delivery implant to the development of cancer vaccines" (PolyMASC web-site). PolyMASC brings polymer coupling. Combined the partners will develop "a drug delivery system for the inoculation of cancer patients." (PolyMASC web-site).
Genzyme (USA)	September 1996	Licensing	Evaluate the application of PolyMASC's PEGylation techniques to Genzyme's gene delivery systems.
Oxford Molecular (UK)	March 1997	Strategic Alliance	Oxford Molecular to provide drug design services to enable PolyMASC to develop a blood growth factor free of third party patent hindrances.
Shearwater (USA)	March 1997	Outsourcing of Manufacturing	Shearwater are specialists in the manufacture of PEGs. They will manufacture PolyMASC's PEGs to enable production of clinical grade activated PEGs
Onyx Pharmaceuticals (USA)	June 1997	Licensing	Onyx are developing novel cancer therapies. PolyMASC's PEGylation techniques will act as a complement to Onyx's products.
NOF (Nippon Oil and Fats of Japan)	June 1997	Strategic Alliance	NOF is engaged in the discovery and development of oral drug delivery systems. PolyMASC's PEGylation offers many benefits in oral delivery.
T.K.T. (USA)	November 1997	Licensing	TKT are developing a PEGylated protein. PolyMASC are supplying the activated PEG species to manufacture the protein. Shearwater will do the manufacturing.

TABLE FIVE: POLYMASC COMPARED TO SOME BIOTECHNOLOGY FIRMS LISTED ON THE LONDON STOCK EXCHANGE

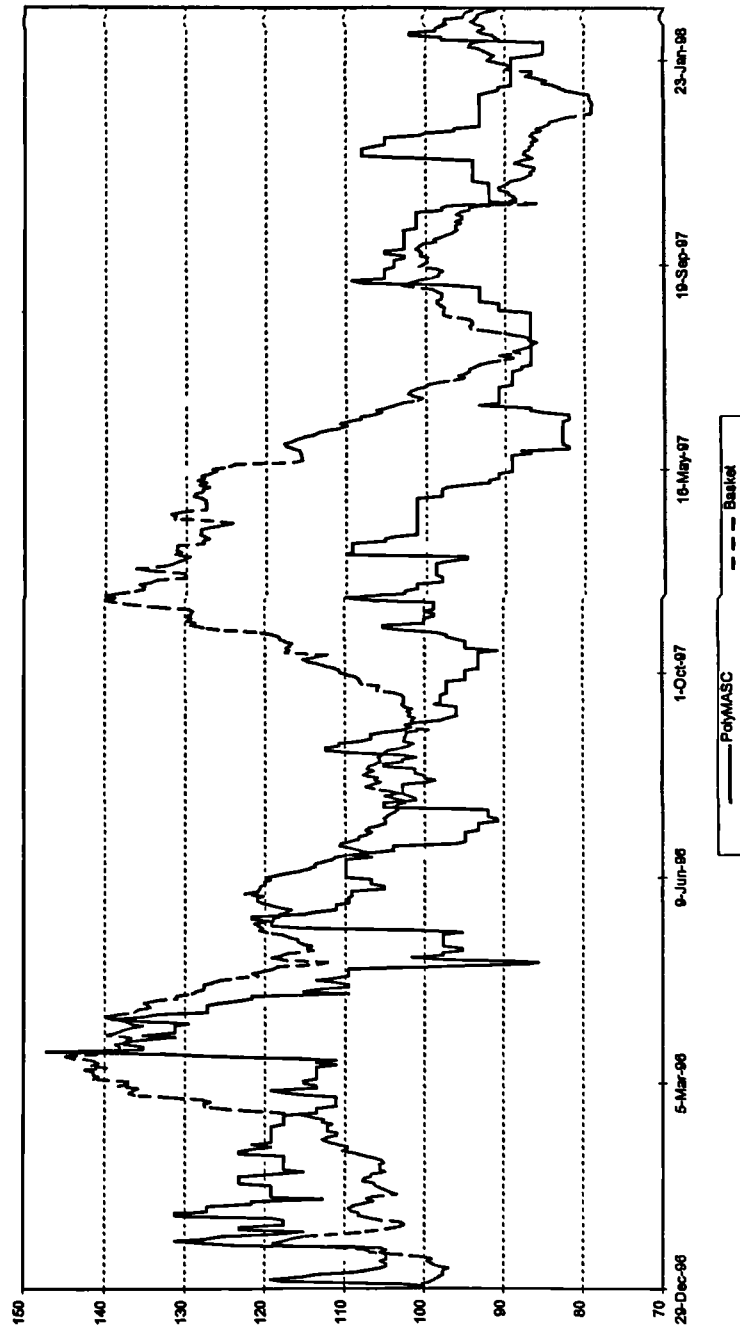
Company	Founded in	R&D Spend in 1996	Number of R&D Alliances	Number of Staff in 1996
PolyMASC	1995	£ 119 thousand	One (with four more formed in 1997)	10
British Biotechnology	1986	£ 29.1 million	One	350
Cantab Pharmaceuticals	1989	£ 6.3 million	Two	91
Cortecs International	1985	£ 12.1 million	Six	166
Chiroscience	1987	£ 5.9 million	Three	170
Proteus International	1987	£ 5.5 million	Three	65

TABLE SIX: LIST OF POLYMASC EVENTS TO MARCH 1998 (as per Extel)

Date	Event
12/19/95	Change in number of shares to 20 million ordinary shares
06/03/96	Director, Lomax, disposes of 6,000 shares at 169 pence
06/07/96	Freemedic's interest is now at 24.27%
06/28/96	European Patents Office accept patent relating to PEG proteins
07/04/96	Bank of Scotland Nominees hold 3%
07/26/96	Bank of Scotland no longer has an interest in the company
08/28/96	Interim results released
09/26/96	European Patent Office Opposition Board re-assures the Company that its patent will hold. Patent relates to tumour targeting of anti-cancer agents and diagnostic products.
09/20/96	AGM. Losses £214 thousand lower than projected in Prospectus
10/11/96	Batten resigns as part-time Commercial Director
10/11/96	Stephen Charles appointed full-time Commercial Development Director
12/04/96	Director, Lomax, sells 14,000 shares at 128 pence
01/27/97	Patent irrevocably upheld
02/04/97	Freemedic now holds 21.475%
02/05/97	Newton UK Smaller Companies Unit Trust now holds 3.5%
02/10/97	Freemedic now holds 18.475%
02/11/97	Newton Investment Management now holds 12.61%
02/17/97	Hydro Med Sciences deal commenced in June 1996 now extended
02/17/97	Bank of Scotland now holds 3.5%
02/25/97	Preliminary results announced
02/25/97	Chairman concludes that the Company is well placed to conduct deals with third parties
03/25/97	Strategic Alliance to investigate Blood Clotting Agents announced with Oxford Molecular
03/25/97	Manufacturing agreement announced with Shearwater of the USA
03/26/97	Dr. Francis sells 12,500 shares at 136 pence. Now holds 15.08%
06/25/97	Strategic Alliance announced with NOF of Japan. Will focus on oral peptide and protein pharmaceuticals.
	Strategic Alliance announced with Onyx Pharmaceuticals. Will focus on development of a novel anti-cancer system.
06/25/97	In the final stages of extending an agreement with Cangene Corporation into PEGylation of Human Growth Factors
06/25/97	Director, Rees, acquired 25,000 shares at 112 pence, now holds 125,000
06/25/97	Director, Harris, acquire 25,000 shares at 112 pence, now holds 175,000
06/27/97	Director, Dutton, acquires 25,000 shares at 115 pence, now holds 25,000
09/25/97	Interim results announced. Turnover has risen and losses reduced
09/25/97	Board continues to be optimistic about the future of the Company
11/24/97	Licensing agreement with TKT of the USA is announced
11/26/97	Henry Ansbacher and Company appointed as an advisor
02/05/98	Preliminary results announced. Group expects rapid growth.
02/06/98	Taylor Young Investment now holds 3.099%

Source: Extel Card

FIGURE ONE: PERFORMANCE OF POLYMASC'S SHARES RELATIVE TO A BASKET OF UK BIOTECHNOLOGY SHARES



Appendix Three

THE OXFORD MOLECULAR CASE STUDY:

Managing inter-organisational collaborative drug discovery projects

INTRODUCTION

“We saw the rush into biotech a bit like the '49 Gold Rush in California. We realised it wasn't the people who rushed into the hills with the picks and shovels like British Biotechnology to try and get the nuggets out who did well, it was Stanfords who built the railroads, the Levi Strausses who sold the tents. We want to be the Levi Strauss of the biotech industry. These guys are up there speculating with their own molecules, but we sell them the tools with which to speculate”

Dr. Tony Marchington, CEO of Oxford Molecular (From Evamy 1998)

Oxford Molecular was founded in 1989 and obtained a London Stock Exchange listing in 1994. The firm has its roots in Oxford University. It was founded by the current CEO Dr. Tony Marchington and his former biochemistry tutor, Professor Graham Richards of Oxford University. Oxford Molecular was one of the first companies to receive seed capital, and sole intellectual property right licenses, from the university's Isis Innovation, a company established to commercially exploit Oxford's research.

The firm has four quite striking features. First is its close links with academia. Second is its Collaborative Discovery division which identifies innovative discovery projects and both brings together and manages virtual teams of scientists from universities and pharmaceutical firms to co-develop individual projects. Third is its leading position in software solutions in drug discovery. Fourth, Oxford Molecular is virtually unique in

the UK biotechnology sector because it achieved a net profit in 1997, albeit on the back of £ 1 million interest receivable.

The firm was originally established to develop and market software to manage the drug discovery process. The drug discovery process is briefly outlined in Table One. Computer technology had become increasingly important in the discovery of new drugs in the late 1980s and its importance has become even more crucial in the 1990s.

INSERT TABLE ONE ABOUT HERE

Informatics⁶³ is particularly important to the future of the pharmaceutical sector. Jan Leschy, the CEO of SmithKline Beecham, commented at a public lecture at City University in June 1998, that informatics, along with molecular and genetic diagnostics, are key to the future of both his company and the industry as a whole. At the heart of Oxford Molecular's current range of software products are Bio-informatics, Chemo-informatics and Computer Aided Molecular Design, which are central to the informatics revolution (see Tables Two, Three and Four for more details).

INSERT TABLE TWO ABOUT HERE

INSERT TABLE THREE ABOUT HERE

INSERT TABLE FOUR ABOUT HERE

Oxford Molecular has been described by some commentators as the Microsoft of the drug discovery sector. It certainly has ambitions to become the industry standard in this sector and has developed a considerable installed base inside both pharmaceutical and biotechnology firms. Dr. Marchington recently observed that:

⁶³ For the purpose of this case we define informatics as the application of computer tools to the drug discovery process. Oxford Molecular's tools aid researchers in the identification of targets to tackle an illness, the process of finding "lead compounds shown to be active against a biological target" and the process of refining a lead into a compound which enters regulatory clinical trials (Annual Report 1997).

“We {Oxford Molecular}⁶⁴ want to make our software and services the industry standard through close alliance with large international partners” (Gracie 1998) and that “You would be hard pressed to find any pharmaceutical research establishment anywhere in the world that does not have Oxford Molecular software at some level” (Ernst and Young 1998).

In fact the company has developed much of its software products through on-site development with leading pharmaceutical firms such as Astra Arcus, Glaxo-Wellcome and Wyeth-Ayerst.

Success in software is only one aspect of Oxford Molecular’s goal to be an industry standard. The other critical aspect is provision of drug services. It is to this end that in 1995 Oxford Molecular formally established its Collaborative Discovery division. This division brings together a diverse range of skills that it offers, under contract, to pharmaceutical and biotechnology companies. The goal of this division is to play a central role in the strategic development of the firm “by winning and managing drug discovery projects” (Annual Report 1997).

The Collaborative Discovery division is of critical importance to Oxford Molecular, and is viewed by its head, Dr. David Ricketts, as the future of the firm. Commenting in 1997 he observed that:

“This group is seen to be the future. Over the next couple of years, within two to three years all being well, we will split the revenue half and half between the two divisions {software and collaborative discovery}.”

An intriguing aspect of this division is that while it only had seven full-timers by the end of 1997 it generated 17.3 % of the firm’s revenues in 1996 and 15.4% in 1997. This is despite the fact that the company employed 175 people in 1997 (Annual Report 1997).

⁶⁴ {} indicates an translation from the verbal to the written word. It provides the context in which the interviewee was speaking.

One of the reasons why the division is seen to be so critical to the long term success of Oxford Molecular is because of the projected size of the markets that the firm is targeting. From Table Five it can be seen that the potential size of the outsourced research market, which the Collaborative Discovery division is targeted upon, is considerably larger than the outsourced IT market, which the software division is attacking. Collaborative Discovery have access to a £900 million market, which is projected to grow some 144% over five years. The software division believes that only 75% of the £500 million pharmaceutical IT market is available to its products. This gives that division a target market of £ 400 million, which is projected to grow by 150% over the next five years.

INSERT TABLE FIVE ABOUT HERE

Another important reason for interest in the Collaborative Discovery division is that it has long term upside potential. In the case of the software division products are sold to customers at a once off profit margin. In the case of the Collaborative Discovery division not only is there a build in profit margin in each contract, but there is also a profit sharing element. Should a drug which the division was involved in discovering make it to the marketplace, then the customer is required to give Oxford Molecular a small royalty payment on each sale. Commenting on the software division Dr. Ricketts observed that,

“as far as I am aware there are no deals done that involve royalties on drugs that may reach the market. So they develop software and sell software products for a good deal.” He later noted that “It is very important to our shareholders to know that we have a deal that involves royalty payments, they don’t know what they are because the partner does not like that to be disclosed.”

Hence one of the reasons why this division is worthy of interest is because of its long term potential to generate not only a half of the company’s turnover, but also the possibility of achieving considerable royalty payments. This would be bottom line

revenue, and while the royalty would be a single digit, it could still represent a sizeable return. As Dr. Ricketts noted:

“If you find a new asthma treatment, or a new obesity treatment, which is something for Alizyme which we are working on, you are talking at least a billion dollar drug, so a few percent is a few tens of millions of pounds.”

The firm believe that they can obtain a considerable share of the outsourced research market. They state that:

“Oxford Molecular believes that the market for outsourced services {both IT and research} could reach £2.2 billion per annum within 5 years. Oxford Molecular, in a synergistic alliance with its recently established partners, Cambridge Combinatorial Ltd and Cambridge Drug Discovery Ltd is well placed to take a significant share of this market” (Annual Report 1997).

According to a report in the *Sunday Times*, Dr. Marchington is aiming for Oxford Molecular to capture between 15% to 20% of the total outsourcing market, which he predicts will have grown to £ 5 billion by the year 2005 (Gracie 1998). This would equate to corporate-wide sales of between £ 750 million to £ 1,000 million per annum. Were Dr. Ricketts’ prediction that Collaborative Discovery will make up half of group revenues within three years to occur then this division would have increased its turnover from £ 1.6 million in 1996 to between £ 375 million to £ 500 million per annum by 2005.

The company believes that to attack this market effectively it is essential to move forward on both the software and services front. The 1997 Annual Report states that the overall strategic intent of the firm is:

“to be the world’s leading supplier of drug discovery solutions through the integration of information technology and drug discovery services including combinatorial chemistry, high throughput screening and genomics”

This case study will focus on the Collaborative Discovery division because of the fascinating insights the operation of this division offers into the new wave of

knowledge based competition which has as its focus inter-organisational co-ordination. The division seeks to integrate multiple forms of knowledge from within Oxford Molecular, its network of partner companies, and university research sub-contractors to deliver high value, knowledge intensive, drug discovery services to pharmaceutical and biotechnology firms. In the context of Oxford Molecular this division is of particular importance due to the rapid internal growth predicted by Dr. Ricketts, the size of the potential external market, and the low levels of staff required relative to turnover. The case will explore what the commercial logic of this division is and how it organises itself to deliver value to its customers. Throughout the case Oxford Molecular's strategy of collaborative discovery is illustrated through two alliances, one with a large Japanese pharmaceutical firm, Yamanouchi, and the other with a small, virtual, UK biotechnology company, Alizyme.

COLLABORATIVE DISCOVERY'S STRATEGIC DIRECTION

Unlike most of the Entrepreneurial Life Science companies listed on the London Stock Exchange, Oxford Molecular does not directly invest shareholder's funds in the independent discovery of novel therapeutic compounds. As outlined earlier it seeks to provide services to other companies in the pursuit of this activity. Provision of software services is one route. The other is a more direct, hands on, participation in the drug discovery process, through provision of managerial or specialist services.

The division can provide customers with specialist technical services such as protein analysis, antibody engineering, high throughput screening and quantitative structure activity relationship services, to mention but a few. These projects are normally of a short duration and are

“aimed at over stretched Drug Design Departments within Pharmaceutical companies who are looking to sub-contract specific projects or companies that currently do not have access to these types of skills and expertise in-house” (Oxford Molecular web site).

The division can also service higher level bespoke research projects in which it plays both a managerial and technical role. These projects may be initiated by either the

customer or Oxford Molecular. For example in the case of their collaboration with Yamanouchi Pharmaceuticals of Japan, it was Oxford Molecular who came up with the initial novel drug target, focusing on Ion channels. It then sold this initial idea as a project to Yamanouchi. Oxford Molecular manage the project on Yamanouchi's behalf in return for contract fees, milestone payments⁶⁵, and a share of future royalties. In the case of its collaboration with Alizyme, it was Alizyme who came to Oxford Molecular with a novel drug target and contracted the company to manage a project to identify and optimise lead compounds that Alizyme could then be taken into the clinical trials. Again Oxford Molecular receives research fees, milestones and future royalties.

In such projects the Collaborative Discovery division brings with it a "wealth of experience and expertise in target identification, screening, synthesis, molecular design and informatics" (Annual Report 1997). More importantly it brings with it a network of contacts through which it can access the skills of leading edge researchers. There are two strands to this network. The first is access to university researchers. This is a key element of the division's original guiding principal.

"The guiding principal for the Drug {Discovery} division is to build a bridge between successful university research projects and the needs of commercial research and development organisations involved in pharmaceutical and biotechnology R&D" (Oxford Molecular web site).

The second important network is its two partner firms, Cambridge Combinatorial and Cambridge Drug Design. Dr. Marchington sums up the importance of these strategic partners, noting that:

"The combination of Oxford Molecular's software and drug design expertise, Cambridge Combinatorial's chemical synthesis skills and Cambridge Drug Discovery's advanced screening capabilities will provide customers with a highly cost effective method of accelerating the drug discovery process" (Oxford Molecular web-site).

⁶⁵ Milestone payments involve a collaborative partner making staged cash payments to Oxford Molecular upon the achievement of specific research milestones.

Oxford Molecular has built up its expertise in drug discovery software through internal growth and over a dozen acquisitions. These acquisitions have brought with them new products, markets and expertise. The Collaborative Discovery division seems to be emulating this strategy to a lesser extent, concentrating more on organic growth and its web of university sub-contractors. Nevertheless, during 1997 the company helped found Cambridge Combinatorial (see Table Six) and Cambridge Drug Design (see Table Seven) taking a minority stake in both firms, with options to buy outright.

INSERT TABLE SIX ABOUT HERE

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The central importance of these firms in the long term success of the Collaborative Discovery division is stated in the 1997 Annual Report. It notes that if the company is to achieve its aim of being a full drug discovery service provider, then it is important that it have four core capabilities, namely informatics, chemical libraries, biological screening and genomics.

Informatics the central capability around which the others are presently organised. This capability has been internally developed by Oxford Molecular. The Annual Report (1997) notes that the

“Oxford Molecular group provides the essential informatics infrastructure that co-ordinates the scientific team. The Collaborative Discovery division provides multidisciplinary research project management and expertise in lead identification and optimisation.”

Expertise in chemical synthesis and combinatorial chemistry libraries is provided by Cambridge Combinatorial. Expertise in biological screening is provided by Cambridge Drug Design. The final key capability is genomics. When discussing the impact of genomics in an press interview Dr. Marchington predicted that:

“about 60% of the new drugs targets will emerge from these disciplines. We will be held back if we can’t offer these as well” (Gracie 1998).

Clearly this is an area that the company needs to address in the near future. The 1997 Annual Report echoes this sentiment, noting that:

“at an appropriate stage, genomic capability, will be added to augment the combinatorial chemistry and high throughput screening services”

COLLABORATIVE DISCOVERY’S FINANCIAL STRATEGY

The overarching financial strategy of Oxford Molecular as a whole is risk aversion. A strong profit margin is sought on each software transaction, or collaborative project. This strategy has played a strong role in the company achieving profitability in 1997. The 1997 Annual Report sums up its financial strategy as follows.

“The company’s low risk strategic principal is to provide solutions targeted to assist in all stages of pharmaceutical research. All products and services are supplied to customers in a way that generates attractive margins for Oxford Molecular, together with, if applicable, milestone payments and future pharmaceutical royalties.”

This risk aversion is mirrored in the Collaborative Discovery division. All projects involve payment of research fees by the collaborative partner (client) to cover not only the division’s costs but also a minimum profit margin. Additional profit may be obtained through the attainment of milestones, and/or through a single digit royalty payment should the customer’s drug eventually make it onto the market. Research fees are paid for the management of the project, regardless of whether milestones are achieved. In a business which had made losses since its inception up to 1997 a key financial imperative is cash. Dr. Ricketts commented that “our reemit here is always to get money in as quickly as possible.” This reduces both the risk of default by a customer, and the cost of financing debtors.

The emphasis on a low risk, profit per deal strategy, is reinforced by the division’s non reliance on milestone payments and royalties as a route to profitability. Dr. Ricketts noted that:

“For us royalty and milestone payments are really just the icing on the cake. We never risk, or speculate {on collaborative projects}. We always make a very reasonable profit on just doing the research project {by ensuring that research fees exceed costs and include a profit margin} ... for the foreseeable future cash is critical both for the company and for my group.”

The method by which the financial structure of a project is negotiated with a collaborator reflects this aim of achieving a healthy profit margin from research fees alone. In an interview with Dr. Ricketts he outlined how the level of research fees was negotiated with Yamanouchi one of the first large deals concluded by the Collaborative Discovery division. The pricing of the deal started on the premise that Collaborative Discovery did not want to risk any of its own shareholder funds on the deal. First, the division calculated what were the internal overheads it would incur in the management of the collaboration. Second, it established what would be the fees that it would need to pay to its university sub-contractors to complete the task assigned to them. This gave Collaborative Discovery an estimate of the cost of the project. To establish the level of margin to charge, the company compared these costs against those that Yamanouchi would have incurred if it did the project independently. Dr. Ricketts says that he

“then went to get an estimate of what their costs would be to do this thing in-house, assuming they had all the know-how. That was a lot more than ours, because we are keeping overheads low by out-sourcing via virtual teams ... You can set the price somewhere in between the two to ensure you get a reasonable margin. You could also argue it is going to cost Yamanouchi X to do this, if they have the know-how. You can say they don’t have the know-how so it is going to cost them a premium. So it is going to cost them two times X, which in general terms doesn’t fly at all. Then you actually ask yourself how do you want to make money on this. What is the nature of the project. Are there going to be very well defined milestones with a value to the partner good enough for them to pay you a lot of money and if so how do you value them?”

The task is then to negotiate with the partner the split of research fees (which must always exceed costs, a safety margin for error in cost calculation, and a profit margin), milestones and royalty payments. Royalties are of the least importance given the length of time to market of a drug and also the high probability that the compound may not make it to market⁶⁶. When referring to the Yamanouchi deal Dr. Ricketts said:

“royalties are very much non-immediate. They are not going to happen for ten years and by and large they are beyond our control ...”

Having established the broad strategic direction of the firm and its financial logic this case will now turn to the questions of why do pharmaceutical and biotechnology firms come to the Collaborative Discovery division, rather than conduct a project in-house, how does it deliver its services to the customer, and how successful is the division?

WHY COLLABORATIVE PARTNERS COME TO THE DIVISION

The Collaborative Discovery division has engaged in many major drug discovery projects. Nine of these projects (for which there were public details) are outlined in Table Eight. An important question to ask is why do such firms choose to outsource part of their research to Oxford Molecular? In the case of the small biotechnology firms the answer is simple. It is due to a lack of financial, or physical, resources and/or a lack of technical, or organisational, capabilities. As Dr. Ricketts put it:

“a small biotech {comes to us} because they don’t have the know-how to do {a particular element of the discovery process} internally and they don’t have the cash to buy in that know-how internally at their current resource level. They don’t want to spend money on hiring somebody full time and buying a computer and software to do it. It is cheaper to come to us and they can get to {the next stage of the discovery process} quicker.”

INSERT TABLE EIGHT ABOUT HERE

⁶⁶ Estimates on the likelihood of a compound that enters clinical trials making it to the market vary from one in five upwards.

The reasons why a large pharmaceutical firm would be attracted to the Collaborative Discovery division are more complex. It is not a question of a large pharmaceutical firm lacking knowledge about Rational Drug Design, Combinatorial Chemistry, High Throughput Screening, or management of projects across universities and commercial organisations. Large pharmaceutical firms have all these skills and where there are gaps in their knowledge pools it would be possible to buy them in, given their vast financial resources. Many of the larger firms spend over \$ 1 billion per year on Research and Development. Instead Dr. Ricketts identifies three broad reasons. The first two reasons essentially conform to the concept of strategic focus, while the third confirms to the concept of technology options.

First are spillovers. A unit within the pharmaceutical firm may have an area which they wish to research, but due to other projects lack time to commit internal resources to the project. Dr. Ricketts provides the following hypothetical example of this effect.

“If I speak to a biologist at Glaxo-Wellcome and ‘say why would you come to me to get some chemistry?’, he would say ‘well because I can’t ever get some of the time from the guys in my lab because they would be working on something else.’ So they never have any time to do something {outside the direct realm of their current project} to test something out, to do a little bit of {additional} work because they are working on something else.”

Second, there are technological gaps which the pharmaceutical firm is aware of and decides it needs to fill. These may be specialist techniques which the firm needs to complete a single project, or alternatively which it needs to acquire and absorb into its future drug discovery methodologies. To this end it may seek out a specialist firm, such as Oxford Molecular, from which it can fill the gap for a single project, and/or engage in technology transfer. Examples of this kind of collaboration would be the Dainippon Pharmaceuticals and Yamanouchi projects where the Collaborative Discovery division is not only managing the project, and providing specialist drug discovery services such as Computer Aided Molecular Design and Combinatorial Chemistry, but is also enabling these capabilities to be transferred to its clients through intensive reporting and on-site training of the customer’s staff.

Third is the search for new technologies. Essentially the large pharmaceutical firm engages in a diverse range of alliances to explore new and emerging drug discovery technologies and methodologies. Technology is moving very quickly and can be costly to implement. Through these alliances the pharmaceutical firm is able to see the technology, or methodology, in action and then decide whether it needs to develop this capability internally, or whether it is peripheral to the company's strategic focus and can therefore be out-sourced. When referring to these kind of technology search alliances, Dr. Ricketts commented that the pharmaceutical firm:

“will want to hedge their bets and make sure that they go for the right {technology or methodology} and that is another reason for making sure that they ally with someone like our group” {who is involved at the frontiers of Rational Drug Design, Combinatorial Chemistry, and High Throughput Screening}.

So essentially collaborators choose Oxford Molecular to fill gaps in their technological capabilities, with the aim of applying these to an individual project, or engaging in technology transfer.

MANAGING THE VIRTUAL FIRM AT COLLABORATIVE DISCOVERY

Virtual Company

The Collaborative Discovery division operates very much as a virtual firm. It has a small staff, with limited resources, therefore to manage large scale discovery projects it relies on its network of partner firms and university sub-collaborators. An immediate benefit of such a system, as previously noted by Dr. Ricketts, is that the division “... keeps overheads low by out-sourcing via virtual teams.”

This virtual structure should not be confused with the concept of a broker. As noted earlier the guiding principal of the division is to act as a bridge between university and commercial R&D, however, while a broker plays a passive role bringing interested parties together and then withdrawing from the day to day operation, the Collaborative

Discovery division plays an active role in the design and management of each discovery project. This distinction between broker and virtual firm is strikingly captured in an encounter with Yamanouchi, which Dr Ricketts recalls.

“When we signed the deal {with Yamanouchi} people came here and said ‘well where are your labs’, and we said ‘well we don’t have any because it is all out sourced.’ And they said ‘well you are just a broker then aren’t you’, and we said ‘we are not a broker. We are a lot more involved in turning an idea into something that is real.’ Our role is essentially having put the couple together, to co-ordinate it. On the scientific level and on the commercial level.”

The method by which ideas are converted into reality by the Collaborative Discovery division is illustrated by Dr. Ricketts when he outlined the operation of the Alizyme project. Tasks are sub-divided and co-ordinated by the division as follows.

“We do the design work in-house, that is the molecular design work. We out-source the chemistry and the biology. The chemistry is done at Cambridge University and the biology, the screen work, is done at Southampton University. We basically identified the people who knew the right chemistry, the people who knew the right biology to do the work. In the end we have a contract for a certain level of staff, for certain lengths of periods to do that work.”

Inter-disciplinary team work

The nature of the Collaborative Discovery division, as a virtual firm, requires that it embraces an inter-disciplinary approach. To manage projects the division brings together a diverse set of skills from within the company itself (expertise in design and software), its partner firms (expertise in HTS and Combinatorial Chemistry) and university sub-contractors (diverse range of chemistry and biology expertise) to deliver its discovery services. This reliance on inter-disciplinary team work is, in part, born from disappointments of the Rational Drug Design approach during the 1980s. It has been realised that a drug cannot be first designed in theory without regard for the practical problems of chemical construction and biological compatibility, rather it

needs to be integrated with other key functional approaches. Dr. Ricketts noted that such integration is present in the division's approach.

“One of the historical criticisms of Rational Drug Design is that you can design things that nobody can make and so people started writing big software programs that were actually turning out to make something which was, I think, pretty much nuts. The way we manage the process is that we will get somebody who will look at a structure and start the design process, but we also work with a lot of chemists as well, because quite often you get to a conflict where you have your Rational Design saying that this fits perfectly and your chemist saying ‘OK but I can't make it, not in a million years.’ It is very much a co-operation. It takes months to get to the point where you get something that is going to have the right shape and properties to interact with your target and something that you can make in a reasonable way.”

For an interdisciplinary approach to work it is necessary for the division to pro-actively manage its relationships with sub-contractors, who provide critical skills which the division, or its partner firms, lack.

Management of sub-contractors

Once a project has been identified the Collaborative Discovery division determines what resources and capabilities will be needed to deliver a successful outcome. This involves deciding what tasks will be conducted in-house and what will be sub-contracted either to its two partner firms or university sub-contractors. In identifying suitable university sub-contractors the division draws upon its knowledge of, and relationships with, academia. Many projects can involve sub-contracts with more than one university. In the case of the Yamanouchi project sub-contracts for services exist with the University of Oxford and AMU in Cambria, Australia. There are three important aspects to these relationships which should be of interest to the reader, namely, the broad nature of the contract, the responsibilities of the contractor and the managerial interaction between the sub-contractors and the division.

Contacts are drawn up between academics who have the required expertise and the company. These academics are referred to as the principles. The practicalities of the contract process were outlined by Dr. Ricketts as follows:

“In terms of a contract, we have an agreement with each university to provide the correct number of people, who are suitably qualified, to work in the right department to work on this project full-time and we have consulting agreements with the principles.”

Oxford Molecular does not micro manage these sub-contractors, charging them with the responsibility of day to day operation of their part of the project. The scientific progress of the sub-contractors is reviewed by a project manager weekly. When outlining the responsibilities of the chemistry sub-contractors in the Yamanouchi project Dr. Ricketts observed that:

“They are really charged with just getting on and doing it. The chemists know chemistry. There are regular internal meetings that involve our partner where we agree on a more weekly scientific basis where to go next and what has happened and review the data. I don’t get involved in telling them what to make, or how to make it.”

One of the reasons for this hands off approach is that these sub-contractors are experts in their field and are contractually charged with delivering specified outcomes, thus negating the need for operational management on the part of Oxford Molecular. Another reason is that often these university sub-contractors are actually involved in the initial design of the project. In the case of the Yamanouchi project Dr. Ricketts outlines his role, and the role of the division as follows.

“I attend the {weekly review} meetings and I contribute to the science where appropriate, but the actual day to day management of the chemist is left to the principles, and the originator of the whole project, who is a pharmacologist, is charged with the overall scientific management, scientific direction. So he will look after his team of managers, who are essentially the principles, who then individually manage the people who do the bench work.”

Thus it can be seen that the role of sub-contractors is very much in the mode of dedicated experts who are part of a wider virtual firm, tied together by legal contracts, but also a bond of scientific expertise and partnership in the delivery of an integrated drug discovery service.

Customer Relations and Interactions

Oxford Molecular provides an additional critical link in this web of partners, making it the central partner in the web. It is Oxford Molecular who provides the communication and managerial systems which link the sub-contractors, partner firms, and the collaborative partner (client) together. As has been outlined earlier in the case there are compelling reasons why collaborative partners come to Oxford Molecular. The communication process between the Collaborative Discovery division and a collaborative partner does not end once agreement to fund a project has been signed. The partners continue to play a pivotal role in the overall strategic management of the project. It is also critical to the success of a project that the collaborative partner be kept informed on the progress of the project. Thus the division pays particular attention to the management of communication with the client.

The level of day to day communication varies from project to project. This is a function of nature of the project, and both the proximity and managerial style of the client. In the case of the Yamanouchi project there is extensive communication. This is because an integral part of the project is technology transfer, which requires intensive communication. It is also a function of the fact that Yamanouchi are based close to the Oxford Molecular Headquarters, and the desire of the Yamanouchi management to receive regular reports on the progress of the project. Formal objectives are agreed between Oxford Molecular and Yamanouchi regarding the progress of the project every six months at strategy meetings. Between these meetings Yamanouchi is kept informed of progress. Dr. Ricketts notes that

“There is a lot of communication {between Yamanouchi and Oxford Molecular}. Yamanouchi have a group that is based not far from here. There are about half a mile from this office. They act as an interface with Japan.

Objectives don't get formally changed between strategy meetings. They may get changed at a meeting, and they may not. There is always {interaction}, it is really a communication process between them and us. They want to know where we are {relative} to the objectives we agreed at the last meeting."

The six monthly meetings are more in-depth. Progress for the previous six months is discussed and directions for the future outlined. Central to these meetings is the transfer of technology and processes. A crucial aspect of the successful management of the project is that Oxford Molecular clearly communicates to its client how it is progressing towards the achievement of the project milestones. If a milestone has been achieved then the firm needs to clearly communicate to the client that this milestone has been achieved and that the results are replicable (where required). This may involve multiple meetings. Dr. Ricketts offers a detailed insight into this process.

"We have the six monthly meetings in which we give a very detailed report of all the work that has been going on and all the descriptors, chemistry, biology, pharmacology, screening, and there is usually a report about {one to two inches} thick. They will usually take about a month to digest that and come back to us with questions. Once those are addressed then part of the process is complete. We also have the strategy meetings. The occasional video conference. So in a way the technology transfer process is implicit within the communication process. Also there are defined milestones on technology transfer, i.e. once they have succeeded in getting something working in their lab which works in our lab then we have success. That covers the whole breath of disciplines. Something else we like doing is to have staff work in our labs from Japan, or send our staff to work in Japan. So they will be sending staff over to work within certain departments for a few months to learn techniques."

The client also plays a role in determining the strategic direction of the project as research results emerge. The partner may wish one research path, which emerges during the discovery process, to be pursued in preference to other options. This scenario is practically illustrated in the design of screens as part of the Ion channel project funded by Yamanouchi. Dr Rickets noted

“That’s very much a collaborative effort {development of screens}. There again we are pursuing a number of different approaches to these screens because high power screens are very tricky to do and the problem is non-trivial. So we are pursuing a number of different approaches and at our last meeting we had basically pretty much assumed that one of them was going to be the right one to use and we made that recommendation to Yamanouchi. But of course they have different criteria. They are in general not very keen on using anything that is radioactive but it turned out that that was probably the best way to go. So it is always a case of aligning what we have with what we need.”

It can be seen that that for a project to succeed it is necessary for the Collaborative Discovery division not only to initiate projects, manage a web of sub-contractors and partner firms to physically work on various aspects of the project, but also to manage relationships with the client clearly indicating progress, managing expectations, and managing the evolution of the project to the overall strategic direction of the collaborative partner.

Before turning to an assessment of the determinants of success for the division a brief summary of the Yamanouchi and Alizyme collaborations are provided. These alliances have formed the back bone of this case.

YAMANOUCHI AND ALIZYME COLLABORATIONS

These two projects commenced in 1996, soon after the formal establishment of the division in 1995. They are fascinating examples of the work of the Collaborative Discovery division because together they illustrate the breath of the projects which the division co-ordinates. Key features of these collaborative projects are compared in Table Nine.

INSERT TABLE NINE ABOUT HERE

The first thing to note is the vast size difference between the collaborative partners. Alizyme is a small virtual UK biotechnology firm. This project is an interesting example of one virtual firm out-sourcing a critical aspect of its business to another.

Yamanouchi, on the other hand, is one of the larger pharmaceutical firms in Asia. These initial differences in size may partially help to account for the contrasting nature of each project.

As a virtual firm itself Alizyme initiated the outsourcing of the discovery process to Oxford Molecular. It is not interested in technology transfer from Oxford Molecular, rather it seeks to access and apply the division's capabilities in drug discovery to its goal of tackling obesity disorders. Given that it does not have a substantial internal set of drug discovery and development resources and capabilities it makes sense to out-source, rather than internalise. Yamanouchi is a large organisation with considerable experience in drug discovery and development, thus a key aspect of its relationship with Oxford Molecular is to learn new drug discovery techniques and internalise them for future use. As a large firm it had many project options which it could have pursued internally, thus it was Oxford Molecular who initiated the first contact regarding collaboration, attracting the larger firm's interest and eventual commitment to the project.

The focus on technology transfer in turn explains why Yamanouchi is more actively involved in the communication process with Oxford Molecular than Alizyme. To transfer new knowledge and capabilities it is necessary for the employees of Yamanouchi to interact closely with Oxford Molecular so that they can learn and internalise the new technology.

The differences in project focus account for the differing methodological approaches. This in turn may account, in part, for the different contributions of the collaborative partners. The financial arrangements are similar, except that the Alizyme project involves one milestone payment, while the Yamanouchi project involves nine. The greater number of milestones in the case of Yamanouchi is due to the existence of milestones related to scientific goals, such as discovery of an active compound, and technology transfer milestones.

The differing nature of these projects is not a problem, rather it is an opportunity for the division. The division offers tailored drug discovery solutions, thus its managerial systems are designed to manage diversity. Each project involves different sub-contractors, a different goal, and different degrees of communication. To date the division has successfully obtained research fees from both partners and the projects continue to progress well. The success of these projects illustrates the ability of the division to deliver its services as a virtual firm by managing a diverse web of partner firms, sub-contractors and clients.

THE SUCCESS OF COLLABORATIVE DISCOVERY DIVISION

Essentially there are three interconnected levels of success for the division. The first is that the project attains its underlying scientific goals. These goals will have been determined at the start of the project, though they may evolve through a process of negotiation with the collaborative partner during the evolution of the project.

Having achieved the basic scientific goals of the project the second and third metrics of success are essentially outside the control of Oxford Molecular and are in the hands of the client. The second metric of success is to take a compound from discovery and into drug development. Drug development is an expensive process and for many reasons a client may decide not to enter a compound into clinical trials. These reasons may not be due to a failure in the project on the part of Oxford Molecular. As Dr. Ricketts notes:

“There are different goals of success. For the Yamanouchi deal, success is getting compounds that are active and selective and they may fail in development for a million reasons and that wouldn’t be down to our project work or the science we use ... You appreciate that any drug that makes it into development it is a success. {To enter clinical trials you need} a compound that is not just active and selective, but has also got all the usual animal type properties. There are lots of different levels of success for us. A partner’s failure doesn’t mean that we have failed.”

The third metric of success is if a drug makes it through the discovery and development processes and into the marketplace. In this scenario Oxford Molecular would obtain single digit royalties. When considering this possibility Dr. Ricketts remains mindful that the basic metric of success for the firm remains attainment of the underlying goals of the initial discovery project. He comments that:

“if we meet our goals in a project, and that may be more than just designing an active compound, then it is a success for us. There is another tier of success, where we get a drug to market and we get a nice big royalty stream.”

So has Oxford Molecular been successful to date? On the first metric of success the answer is yes. Collaborative partners are consistently paying Oxford Molecular research fees for the work it does on their behalf. They would not do so if the Collaborative Discovery division did not meet the scientific goals of the project.

On the second metric the firm also seems to have had some success. Its collaboration with NeoRX Corp. on a radioimmunotherapy product was a success at the discovery stage. The product is now in phase II clinical trials. Given that the discovery phase can take many years (PhARMA, 1999, estimated that on average it takes 6 years) it is not surprising that few of the division's projects have entered clinical trials to date. By the turn of the century there should be a clearer picture on the success of the division in discovering compounds which enter clinical trials.

It is probably fair to say that the long term success of the division hinges on managing projects which enter clinical trials. After all the remit of the division is drug discovery and the immediate goal of that process is to discover compounds which enter clinical trials. The third metric, namely a drug entering the market, is not as critical to the long term success of the firm. The reasons why a drug can fail clinical trials are varied, and where these can be managed they are largely in the hands of the developer not the discoverer.

The financial success of the division is masked in the accounts by the consolidation of the results of both the software and discovery divisions in the annual report. As noted

previously the Collaborative Discovery division is delivering an increasing proportion of the company's turnover, while consuming only a small number of the company's internal staff resources. It is not publicly known how much of Oxford Molecular's expenses are attributable to the Collaborative Discovery division. For this reason the case cannot determine the precise profitability of the division. However it can be observed that the Collaborative Discovery division is likely to be profitable in of itself given the earlier comments of Dr. Ricketts on the pricing of collaborative contracts.

CONCLUSION

The Collaborative Discovery division has prospered since its inception in 1995. It has managed to attract an impressive portfolio of collaborative partners. It has successfully enlarged its access key resources and capabilities necessary to deliver a broad range of drug discovery services via a web of partner firms and university sub-contractors. A major threat to the commercial success of small biotechnology firms, identified in the Ernst and Young *European Life Sciences 98* report, is that of technology consolidation. They warn that firms which rely on a single technological expertise will have grave difficulty in continuing to attract pharmaceutical partner firms, from which they can extract high profit margins.

The Collaborative Discovery division has successfully expanded its technological expertise in informatics to a broader range of technological capabilities through its virtual network. The future of the division appears bright if it can build on its current technological capabilities, manage its network, and expand its technological base to include a genomic capability. As Ernst and Young observe:

“Oxford Molecular has helped establish and nurture daughter companies in the high throughput screening and combinatorial chemistry areas to complement its in-house informatics expertise - it just needs to link up with a genomics company and it will be able, through its network, to offer potential big pharma partners a comprehensive array of discovery tools.”

Oxford Molecular remains on track to becoming a one-stop provider of drug discovery services and thus fulfilling its goal of capturing a significant share of this rapidly expanding market.

TABLE ONE: THE DRUG DISCOVERY PROCESS

The goal of the drug discovery process is to create a drug compound, targeted at a specific disease which can enter regulatory clinical trials. Should the drug successfully pass through the regulatory process then it can be marketed. At the heart of the Oxford Molecular approach to drug discovery is an embrace of both traditional drug discovery and computer based Rational Drug Design. The difference between the two approaches is that Rational Drug Design seeks “to model the molecular structure of the target of a drug, and then design a drug molecule which will fit it. This contrasts to the alternative, which is to screen a large number of compounds for drug activity, choose the most promising and make a whole lot of variants, choose the most promising of them and repeat until a suitable drug is found” (Bains 1993).

In practice it is not possible to create a drug compound employing computer methods alone, thus Oxford Molecular offers its customers a combination of software to facilitate Rational Drug Discovery, in addition to managerial skills and experience in the blending of this technique with traditional methods of screening and discovery.

There are four broad stages to a drug discovery process, three of which Oxford Molecular are actively involved in. The first is the identification of a **target disease**. Targets may be selected on the basis of specialist knowledge about the disease within a firm, the potential market rewards of pursuing a treatment, and/or new advances in technology which offer potential application in a targeted disease area. Targeting a disease is generally the domain of Oxford Molecular’s clients.

Second is **identification of biological targets**. These are proteins or genes which the researchers believe play an important role in the spread of the target disease. The researchers seek to understand what form of compound would be needed to interact with the protein or gene which is causing the disease and thus manage or cure it.

Third is **lead compound identification**. This involves identifying compounds which are biologically active against the biological target.

Fourth is **lead optimisation, or refinement**. Having identified a number of biologically active compounds it is necessary to determine which of these has the best mix in terms of activity, with the lowest level of toxicity.

TABLE TWO: BIO-INFORMATICS - IDENTIFICATION OF BIOLOGICAL TARGETS.

“Bio-informatics is the use of software, databases and on-line resources to store, retrieve and analyse genomic information (e.g. information on human genes). Analysis of genomic information enables suitable biological targets to be identified in order to discover new drugs which may halt the disease or control the infection” (Annual Report 1996).

Bio-informatics software produced by Oxford Molecular is used by researchers as “tools for the analysis of DNA and protein sequence data.” (Oxford Molecular web site). Bio-informatics tools play a central role in the **identification of biological targets**.

Examples of Bio-informatics products offered by Oxford Molecular include: AbM TM (for humanising anti-bodies), MacVector [®] (DNA and protein sequencing), and OMIGA TM (a set of sequence analysis tools which operate under Windows 95 TM). Details on these and other products available from Oxford Molecular may be obtained by referring to the company’s excellent web site: <http://www.oxmol.co.uk/prods>

TABLE THREE: CHEMO-INFORMATICS - THE IDENTIFICATION OF LEAD COMPOUNDS.

Chemo-informatics, builds upon the process of identifying biological targets (central to which is Bio-informatics) with the goal of identifying **lead compounds**.

Chemo-informatics software tools enable researchers to “capture, analyse and communicate the increasing volumes of biological and chemical data available in the search for new lead compounds and drug candidates” (Annual Report 1997). These tools are used for “selecting, comparing, relating, mining data for databases of chemical compounds, structures, properties and biological assay results.” (Oxford Molecular Web site).

Examples of Chemo-informatics software available from Oxford Molecular include: RS³™ Discovery (which is used for “storing, searching and retrieval of chemical structures in addition to chemical and biological properties, experimental data and registration” Oxford Molecular web site), and DIVA™ (a spreadsheet based product to facilitate the visualisation and analysis of chemical structures).

TABLE FOUR: COMPUTER AIDED MOLECULAR DESIGN (CAMD) - LEAD OPTIMISATION

Lead optimisation involves analysing the compound to discover its potential biological activity and toxicity. When a lead compound is identified it still remains to be proven whether this compound can be safely applied to humans, and whether it successfully tackles the disease. The compound may well need to be structurally modified to enable it to both safely and effectively combat the disease. Once the researchers have modified the lead compound it must then be entered into clinical trials before it can be marketed. These trials can cost hundreds of millions of pounds. If the compound fails in trials then it cannot be sold to the public. It is therefore vital that the process of lead optimisation discovers potential problems with the compound, and solves these, prior to entering into clinical trials. CAMD greatly enhances the efficiency and effectiveness of the lead optimisation process when compared to older, conventional screening techniques.

“In the past this {lead optimisation} involved random chemical synthesis around a particular lead structure with known, but inadequate, biological properties {CAMD} .. allow{s} a more rational approach whereby a research scientist can visualise a compound's structure through molecular modelling and explore structural modifications to improve its desired properties” (Annual Report 1996).

CAMD tools are “used both by computational and experimental chemists to predict reaction mechanisms and explain interactions, speeding up the identification of compounds with desirable properties” (Oxford Molecular web site).

Examples of CAMD tools available from Oxford Molecular include: Tsar TM (chemical spreadsheet to analyse structures and properties of compounds), TOPKAT TM (computational toxicology tool), and Unichem TM (molecular modelling package).

**TABLE FIVE: MARKET FOR OUTSOURCED SPECIALIST DRUG DISCOVERY
IT AND SERVICES**

Market	1996	2002	% Growth
Out-sourced IT	500	1,300	160
75% of IT outsourcing available to Oxford Molecular	400	1,000	150
Out-sourced Research projects	900	2,200	144
Total Accessible Market	1,300	3,200	246

Source: Oxford Molecular Annual Report 1997

TABLE SIX: CAMBRIDGE COMBINATORIAL LTD (PRIVATE, UNLISTED, COMPANY)

Foundation

The company was founded in February 1997 by a group of former Pfizer scientists and professors from Cambridge University and the University of Southampton. Oxford Molecular, invested £ 2 million for a 19.99% shareholding. The other shareholders are the senior management, including Allan Marchington as CEO (the brother of Tony Marchington, CEO of Oxford Molecular), and Cambridge University, who provided intellectual property rights. In August 1997 Oxford Molecular invested a further £ 2 million in the form of preference shares. The firm has the option, through to December 1998, to purchase the company's equity outright.

Technology

The company takes a medicinal chemistry approach to drug discovery, providing chemical synthesis services. It specialises "in the design, production and supply of chemical structures for the drug discovery industry" (Oxford Molecular web-site). It can produce "moderately sized libraries of up to 20,000 compounds in a pure, well characterised reproducible form. Milligram batches of each component in a library will be produced at the same time to provide the end user with sufficient material for every stage of testing" (Oxford Molecular web site). Such libraries play a crucial role in generating a pool of compounds from which lead compounds can be identified.

Commercial Offering

Combinatorial chemistry services, consultancy, and technology transfer.

Collaborative Relationship with Oxford Molecular

Cambridge Combinatorial plays an important role in Oxford Molecular's long term aim of providing one-stop-shopping for drug discovery services. This goal requires four capabilities, one of which is chemical synthesis and combinatorial libraries (Annual Report 1997). The Collaborative Discovery Division manages projects which identify novel drug targets to which Cambridge Combinatorial's technology can be applied to generate a library of potential lead compounds. In turn Oxford Molecular's (and partners') capabilities in screening chemical libraries and rational drug design enable these leads to be optimised before entering clinical trials.

Deals to Date

Cambridge Combinatorial has combined with the Collaborative Discovery division in three important alliances. The first aims to provide combinatorial library designs and synthesis, including technology transfer, to Dainippon Pharmaceuticals of Japan. The second alliance is with Oxford Glyco Sciences. This is targeted on "carbohydrate processing enzymes which have potential therapeutic use for diseases such as fungal infections" (Oxford Molecular web-site). Cambridge Combinatorial provide synthesis of libraries, which are designed using expertise from Oxford Molecular, while the libraries are screened by Cambridge Drug Discovery. The third collaboration seeks to "identify novel lead compounds for the treatment of metabolic disorders" for Mitisubishi Chemical Corp. (Oxford Molecular web site).

Sources: Oxford Molecular: <http://www.oxmol.co.uk>, the 1997 Annual Report, and Cambridge Combinatorial's profile - http://www.xenseo.com/conference/hsw/camb_comb.html

TABLE SEVEN: CAMBRIDGE DRUG DISCOVERY LTD (PRIVATE, UNLISTED, COMPANY)

Foundation

The company was founded in December 1997 by four former Pfizer scientists. £ 5.25 million was raised from investors, primarily Oxford Molecular, who invested £ 5 million: £ 2 million in return for a 19.99% shareholding, £ 2 million as a secured loan, and a £ 1 million in preference shares. If Cambridge Drug Discovery is floated, or sold, then the preference shares convert into a 10.1% shareholding. Oxford Molecular has the option, exercisable between 2000 and 2002, to purchase the remaining Ordinary Shares for the greater of 3 times of turnover, or 15 times net profit.

Technology

High Throughput Screening (HTS), the firm's core technology, enables researchers to screen libraries of molecule compounds against biological targets (e.g. proteins) to determine how potentially potent, selective and bio-available the compounds are as a new drug candidate. Biological screening, using HTS, is central to the task of identifying lead compounds.

These libraries can contain millions of compounds, hence automation is essential in the screening process. Cambridge Drug Discovery has invested in robotics systems which enable the firm to "screen up to 100,000 compounds a day from customers own libraries of chemical compounds against either novel or non-proprietary targets" (Oxford Molecular Web Site).

Commercial Offering

The company can screen libraries for customers in addition to the design of chemical assays and HTS consultancy.

Collaborative Relationship with Oxford Molecular

Much of the firm's products will be sold via collaborative projects with Oxford Molecular. Third party sales will be through Oxford Molecular's distribution system, for which Cambridge Drug Discovery pays a percentage of the overheads. As outlined in the Oxford Molecular Annual report (1997) HTS is one of the four capabilities needed to achieved the firm's goal of becoming a one-stop-shop provider of drug discovery services. The Collaborative Discovery division manages projects which identify novel drug targets to which Cambridge Drug Discovery's HTS technology can be applied to generate lead compounds. In turn Oxford Molecular's capabilities in rational drug design enable these leads to be optimised before entering clinical trials.

Deals to Date

The Drug Discovery Division of Oxford Molecular, in co-operation with Cambridge Drug Discovery *and* Cambridge Combinatorial, is managing a drug discovery programme targeting fungal infections for Oxford Glyco Sciences. Cambridge Drug Discovery will screen the libraries which Oxford Molecular design and develop, with Cambridge Combinatorial conducting the synthesis of those libraries.

Sources: Cambridge Drug Discovery web site - <http://www.camdd.co.uk/> Oxford Molecular web site: <http://www.oxmol.co.uk> and OM's Annual Report 1997.

TABLE EIGHT: COLLABORATIVE DISCOVERY DIVISION PUBLICLY DETAILED PROJECTS.

Collaborator Partner & Task	Start Yr	Details
Alizyme (Multi disciplinary discovery)	1996	Targeting obesity disorders through "identification of novel inhibitors of pancreatic lipase, an enzyme produced by the pancreas to digest fatty foods" (OM web site). OM does in-house design work and out-sources chemistry and biology to university researchers.
Dainippon Pharmaceutical (Combinatorial library designs & synthesis)	1997	OM provides molecular modelling techniques to design novel targeted combinatorial libraries which Cambridge Combinatorial will synthesize. An important aspect of this collaboration is the training and transfer of technical skills to Dainippon staff.
ImmunoGen (Antibody humanisation)	1995-1997	Humanise monoclonal antibody for anti-cancer research. Resurfacing - making surface of an antibody look human - to reduce immune responses. ImmunoGen got exclusive rights to the oncology drug. OM got payment and rights to use ImmunoGen's resurfacing technology outside oncology.
Mitsubishi Chemical Corp. (Drug Design & Combinatorial Chemistry)	1998	OM and Cambridge Combinatorial will "identify novel lead compounds for the treatment of metabolic disorders" (OM web site).
NeoRX Corp. (Computational - antibody humanisation)	1993	Humanised antibody component of <i>Avicidin</i> , a radioimmunotherapy product to localise antibodies at tumour sites. The drug is now in phase II clinical trials.
Oxford Glyco Sciences (drug design, combinatorial chemistry & HTS)	1998	The project targets "the design and synthesis of inhibitors of carbohydrate processing enzymes, which have potential therapeutic use for diseases such as fungal infections" (OM web site). OM will use its software and discovery skills to design multiple libraries. Cambridge Combinatorial will provide synthesis of the libraries. Cambridge Drug Discovery will provide High Throughput Screening (HTS) and consultancy services for Oxford Glyco Sciences' internal discovery process.
PolyMASC (Computer Aided Molecular Design - CAMD)	1997	Oxford Molecular to provide drug design services to enable PolyMASC to develop a blood growth factor free of third party patent hindrances.
Proflix (Computer Aided Molecular Design - CAMD)	1996	Targeting peptidomimetic drugs to treat cancer. Drug candidates developed using CAMD to mimic the actions of natural peptides which block key cell receptors involved in cell proliferation. Proflix contributes HTS of chemical libraries and directed drug design methods.
Yamanouchi (multi disciplinary discovery)	1996	Discovery of a novel drug candidate, which is based on Ion channels, and has the potential to target multiple diseases. The project is managed by OM, with much of the work out-sourced to university researchers.

Source: Oxford Molecular Press Releases: <http://www.oxmol.co.uk>

TABLE NINE: COMPARATIVE OVERVIEW OF YAMANOUCHI AND ALIZYME

	Alizyme	Yamanouchi
Project initiated by	Alizyme	Oxford Molecular
Project focus	Obesity lipase inhibitor.	Novel compounds based on Ion channels.
Goals of Project	Discovery of an active compound.	Discovery of an active & selective compound. Technology transfer.
Size of Collaborator	Market Cap. £ 11.9 m in July 1998. Sales (1997) £ 0 Profit (1997) £ - 3.14 m	Market Cap. £ 3,147 m in July 1998 Sales (97) £ 1,335.78 m Net Profit (97) £ 134.26 m
Contribution of Partner: Financial	Research fees. A single milestone. Single digit Royalty.	Research Fees. Nine milestones. Single digit Royalty.
Other	Overall monitoring and target identification.	Prestige collaborator. Compound library (100,000s of compounds). Interaction on best approaches to screening. Drug development expertise.
Intensity of Partner interaction	Active	Very Active (due to additional technology transfer goal).
Overall methodological thrust of project	Almost a classical form of Rational Drug Design.	A mix of classical drug discovery and Rational Drug Design methods.

Sources: Interview with Dr. Ricketts, Reuters on-line, Annual Report 1997, Oxford Molecular web site

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Appendix Four:

Sample of Events Included and Excluded from Event Study

EVENTS INCLUDED IN STUDY

Company Name	Event Type	Event Date (month/day/year)	Details of Event	Percentage Abnormal Returns on Event Day (mean AB across all six models)
Biocompatibles	Phase II/III Trials	12/29/97	EMA marketing approval of heart disease stents	+ 5.59
Cambridge Antibody Technology	Regional Alliance Gain	03/23/98	R&D alliance with Progenitor	+ 1.18
Cambridge Antibody Technology	Discovery/P I Trials	05/26/98	Monoclonal antibody enters PI trials	+ 1.02
Cantab Pharmaceuticals	Regional Alliance Gain	02/27/97	Research Joint Venture with Marie Curie Cancer Care	+ 2.94
Cantab Pharmaceuticals	Regional Alliance Gain	01/14/98	R&D alliance with Kakestusuke (Prophylactic vaccine for chickenpox and shingles)	+ 2.56
Celltech	Regional Alliance Gain	10/16/97	R&D alliance with Zymogenetics (coronary heart disease)	+ 2.78
Celsis International	Regional Alliance Gain	09/15/97	Five year distribution alliance with Becton Dickinson (systemSURE™ – portable rapid hygiene system)	+ 0.04
Chiroscience	Prestige Alliance Gain	06/27/97	R&D alliance with Schering Plough (Oral Asthma)	+ 6.33
Chiroscience	Prestige Alliance Gain	02/11/98	R&D alliance with Bristol Meyer Squibb (MMP cancer research)	+ 2.06
Chiroscience	Prestige Alliance Gain	03/31/98	License Chirocaine to Zeneca outside the UK	+20.35
Chiroscience	Regional Alliance Gain	04/09/97	R&D alliance with Alcon Laboratories (small molecules)	+ 1.52
Chiroscience	Regional Alliance Gain	09/15/97	Joint Venture with Geron Corp. (genetic R&D into ageing)	+ 1.84
Chiroscience	Phase II/III Trials	12/04/97	Files for EMA marketing approval for Chirocaine	- 1.99

Company Name	Event Type	Event Date (month/ day/year)	Details of Event	Percentage Abnormal Returns on Event Day (mean AB across all six models)
Chiroscience	Discovery/P I Trials	01/05/98	MMP inhibitor enters PI trials	+ 5.98
Cortecs	Prestige Alliance Gain	07/21/98	Marketing alliance with Astra (One Step)	- 2.87
Cortecs	Prestige Alliance Gain	05/18/98	Distribution alliance with Glaxo-Wellcome (Macritonin in Greece)	+ 0.05
Cortecs International	Phase II/III Trials	10/30/97	Osteosarcoma point of care test launched on market	+ 8.31
KS Biomedica	Prestige Alliance Gain	10/14/96	R&D alliance with Hoffman- La-Roche (subsidiary of Roche Holdings) (antibody development)	+ 6.18
KS Biomedica	Phase II/III Trials	02/03/98	Positive PII Rheumatoid Arthritis trial	+35.31
Medeva	Discovery/P I Trials	12/16/98	Positive PI results from Hepagene Hepatitis B trial	+ 9.18
Oxford Biomedica	Prestige Alliance Gain	01/12/98	R&D alliance with Rhone- Ploulenc-Rorer (Gene research into Heart Disease)	+14.58
Oxford Biomedica	Prestige Alliance Gain	12/14/98	Alliance with Rhone- Ploulenc-Rorer to explore application of Oxford Biomedica's Gene technology to RPR.	+21.04
Oxford Biomedica	Discovery/P I Trials	11/17/97	PI cancer trial to begin	+ 0.03
Peptide Therapeutics	Prestige Alliance Gain	12/04/98	R&D alliance with Novartis (Protease inhibitors – application of Peptide Therapeutics' RAPiD technology)	+ 2.33
Peptide Therapeutics	Prestige Alliance Gain	01/05/98	R&D alliance with Pfizer (Veterinary Allergy vaccine)	+ 3.12
Peptide Therapeutics	Prestige Alliance Gain	02/10 97	R&D alliance with SmithKline Beecham (Allergy vaccine)	+11.24
Peptide Therapeutics	Regional Alliance Gain	01/23/97	R&D alliance with Medeva (vaccines)	+17.72
Peptide Therapeutics	Regional Alliance Gain	04/28/98	R&D alliance with OraVax (anti-ulcer vaccine)	+ 3.42
Peptide Therapeutics	Phase II/III Trials	05/14/97	Approval granted by FDA to conduct PII Typhoid vaccine trials	+ 7.28
Phytopharm	Prestige Alliance Gain	08/24/98	R&D deal with Pfizer (Obesity drug)	+10.43

Company Name	Event Type	Event Date (month/ day/year)	Details of Event	Percentage Abnormal Returns on Event Day (mean AB across all six models)
Phytopharm	Phase II/III Trials	05/06/98	Osteo-arthritis enters phase II trials	+ 2.54
Phytopharm	Phase II/III Trials	03/25/98	Positive PIII European trials for Zemaphyte (eczema drug)	+15.30
Phytopharm	Discovery/P I Trials	10/13/98	Appetite suppressant enters PI trials	+ 4.48
PolyMASC	Regional Alliance Gain	03/25/97	R&D alliance with Oxford Molecular (blood growth factor)	+14.26
PolyMASC	Regional Alliance Gain	11/25/97	R&D alliance with Transkaryotic Therapies Inc (PEGylated protein)	+ 7.54
Powderject	Prestige Alliance Gain	03/04/98	R&D alliance with Glaxo- Wellcome (DNA vaccines)	+28.58
Powderject	Discovery/P I Trials	09/16/98	Positive laboratory results on mice for cancer vaccine	+ 1.95
Proteus International	Phase II/III Trials	02/20/97	BSC diagnostic approved for marketing in Ireland	+35.53
Proteus International	Discovery/P I Trials	03/05/98	High blood pressure vaccine passes 'proof of concept'	- 0.03
Scotia Holdings	Phase II/III Trials	09/12/96	PII cancer trial succeeds	+ 1.08
Scotia Holdings	Phase II/III Trials	11/06/97	Amelorad radiotherapy drug submitted to EMA for approval	+ 3.16
Shield Diagnostics	Prestige Alliance Gain	01/23/98	Development and Marketing alliance with Abbott Laboratories (AFT – Activated Factor Twelve – heart disease diagnostic)	+14.33
Shield Diagnostics	Regional Alliance Gain	10/12/98	Distribution agreement with Hitachi Chemical Co. (<i>in vitro</i> allergy blood test)	+ 0.09
Shield Diagnostics	Phase II/III Trials	06/04/97	AFT heart diagnostic test submitted to FDA for marketing approval	+ 9.03
Shield Diagnostics	Phase II/III Trials	01/05/98	Launches CAG. A assay on market	- 1.55
Shield Diagnostics	Phase II/III Trials	09/01/98	Clearance to market AFT heart diagnostic test by FDA	+ 4.90
Shire Pharmaceuticals	Phase II/III Trials	06/17/98	Positive PIII Hyclinda trial	- 0.16
Shire Pharmaceuticals	Phase II/III Trials	07/20/98	Positive PIII Alzheimer's disease drug trial	+ 9.94
Stanford Rook	Phase II/III Trials	06/17/98	Plans to commence PIII lung cancer trials	+14.59
Therapeutic Antibodies	Regional Alliance Gain	10/13/97	Licensing agreement with Altana (Venom treatment)	+ 4.95

Company Name	Event Type	Event Date (month/ day/year)	Details of Event	Percentage Abnormal Returns on Event Day (mean AB across all six models)
Vanguard Medica	Regional Alliance Gain	10/12/98	Elan named commercial partner (Frovatriptan)	+ 4.50
Xenova	Prestige Alliance Gain	02/18/98	R&D alliance with Eli Lilly (Blood clot drug)	+15.1
Xenova	Regional Alliance Gain	12/11/97	Joint Venture with Wallac (drug discovery)	+ 3.67
Xenova	Regional Alliance Gain	01/15/98	R&D alliance with the Institute of Grassland and Environmental Research (Phytochemistry)	+17.58

Number of Events Included in Event Study:

Prestige Alliances = 15
 Regional Alliances = 16
 PII/III trials = 16
 Discovery/PI = 8
 Total = 55

EVENTS EXCLUDED FROM EVENT STUDY DUE TO CONFOUNDING EVENTS

(Confounding events occur within -5 to +5 trading days of the main event)

Company	Event Type	Event Date (month/ day/year)	Details of Event	Date of Confound (month/ day/year)	Details of Confound
Alizyme	Prestige Alliance Gain	07/22/98	Development licensing deal with SmithKline Beecham	07/22/98	License drug delivery from BTG
Alizyme	Discovery/P I Trials	10/21/98	Discovery of obesity compound	10/21/98	Interim results announced
Biocompatibles	Regional Alliance Gain	05/30/98	Distribution deal with Wesley Jessen	05/22/98	Several distribution deals announced
Biocompatibles	Phase II/III Trials	04/10/97	FDA permission to market contact lens	04/14/97	Acquisition of Bio Polymerix completed
British Biotechnology	Phase II/III Trials	03/05/97	Files Zacutex for EMA approval	03/06/97	Announces third quarter results
British Biotechnology	Phase II/III Trials	05/12/97	Positive results from Zacutex PIII trial	05/12/97	Series of marketing appointments also announced
Cambridge Antibody Technologies	Regional Alliance Gain	12/18/97	R&D alliance with ICOS Corp.	12/16/97	Announces discovery of ProAb assay
Celsis International	Regional Alliance Gain	02/12/98	World-wide distribution rights assigned to Becton Dickinson (system SURE™)	02/12/98	Announces expected record profits for year end
Chiroscience	Regional Alliance Gain	05/20/97	R&D alliance with Powderject (local anaesthetic)	05/13/97	Phase I asthma clinical trial commences
Chiroscience	Phase II/III Trials	01/23/97	ADD drug enters PII trials	01/23/97	Agrees with Medeva to continue alliance to purify Methylphenidate
Chiroscience	Phase II/III Trials	04/29/98	Files NDA with FDA for Chirocaine	04/29/98	Announces preliminary results
Chiroscience	Phase II/III Trials	09/29/98	Drug delivery systems moves to PII trials	09/29/98	Discovery of on/off gene

Company	Event Type	Event Date (month/ day/year)	Details of Event	Date of Confound (month/ day/year)	Details of Confound
Chiroscience	Discovery/P I Trials	12/20/96	PI heart disease trial begins	12/18/96	Complete acquisition of Darwin Molecular
Chiroscience	Discovery/P I Trials	05/13/97	PI Asthma trial begins	05/14/97	Chris Evans (co- founder) resigns as Director
Cortecs International	Prestige Alliance Gain	06/12/98	Boehringer Mannheim (subsidiary of Roche Holdings) (rights deal for H-Pylori)	06/08/98	Cortecs CEO resigns
Cortecs International	Regional Alliance Gain	06/12/98	Distribution alliance with Dickinson & Co (Link2 test)	06/08/98	Cortecs International CEO resigns
Cortecs International	Regional Alliance Gain	08/03/98	Distribution alliance with Ferrer Internacional SA (Macritonin ™)	07/28/98	2 members of remuneration committee resign
Cortecs International	Phase II/III Trials	06/30/97	Macrulin to enter Phase II trials	06/26/97	Issue £125,000 shares to exercise share options
Cortecs International	Phase II/III Trials	08/12/97	Bronchitis Phase II trial results positive	08/07/97	Confirms positive PII/III Pan-European Macritonin trial results
Cortecs International	Phase II/III Trials	06/12/98	Helicobacter Pylori rapid test kit approved for marketing by FDA	06/08/98	CEO resigns
Medeva	Phase II/III Trials	10/01/98	Marketing approval for Bladder Cancer drug given by FDA	10/01/98	John Ferguson joins Medeva as a Director
Medeva	Phase II/III Trials	10/28/98	Applies for EMA approval for Hepatitis B vaccine	11/03/97	License granted by UK medical authorities for dry powder inhaler
Phytopharm	Regional Alliance Gain	11/03/97	Distribution agreement with Rallis of India	11/03/97	Distribution agreement with Heska Corp.

Company	Event Type	Event Date (month/ day/year)	Details of Event	Date of Confound (month/ day/year)	Details of Confound
PolyMASC	Regional Alliance Gain	02/17/97	Extension of Hydro Med Sciences R&D alliance	08/24/97	Results announced
PolyMASC	Regional Alliance Gain	06/25/97	R&D alliance with NOF Corp. (oral drug delivery)	06/25/97	R&D alliance with Onyx (anti- cancer)
Powderject	Prestige Alliance Gain	06/09/98	R&D alliance with Zeneca (drug delivery)	06/09/98	Announces undisclosed deal with Japanese partner and losses up by 45%.
Powderject	Discovery/P I Trials	12/07/98	Hepatitis B trial passes PI trials	12/02/98	Awarded European patent coverage for DNA vaccine
Powderject	Discovery/P I Trials	04/20/98	Passes PI trial for needless version of Alpoostadil	04/20/98	Also announces acquisition of minority interest of Psiox joint venture from Pharma Sciences
Proteus International	Regional Alliance Gain	05/02/96	Licensing agreement with Enfer Science (BSC)	05/02/96	Licensing agreement with Janssen Pharmaceutica (veterinary vaccine)
Proteus International	Discovery/P I Trials	04/29/98	Hypertension vaccine passes 'proof of concept'	04/23/98	Launches rights issue
Scotia Holdings	Phase II/III Trials	01/20/98	Swedish regulatory authorities approve reformulation of eczema drug	01/20/98	Swedish regulatory authorities approve reformulation of madtalgia (breast pain) drug
Shield Diagnostics	Prestige Alliance Gain	07/22/97	R&D alliance with Abbott Laboratories	07/16/97	Expects to receive approval for AFT test within 6 months
Shield Diagnostics	Regional Alliance Gain	10/28/98	Distribution agreement with BIOSTAR (point of care diagnostic kits)	11/04/98	Distribution agreement with BIOSITE (rapid immunoassay diagnostics)

Company	Event Type	Event Date (month/ day/year)	Details of Event	Date of Confound (month/ day/year)	Details of Confound
Shire Pharmaceuticals	Discovery/P I Trials	05/06/97	PI trials of ME drug to begin	05/06/97	Also announces progress of a number of other trials
Trinity Biotech	Phase II/III Trials	09/05/98	FDA clearance for 2 infectious disease markers	09/05/98	FDA clearance for 2 infectious disease markers
Vanguard Medica	Prestige Alliance Gain	09/07/98	R&D alliance with Roche (Kidney failure)	09/14/98	Psoriasis drug fails phase II clinical trials.
Vanguard Medica	Regional Alliance Gain	12/10/98	R&D alliance with 3M Pharmaceuticals (liver infection)	12/10/98	Failure of Phase II kidney drug trial.
Vanguard Medica	Regional Alliance Gained	03/16/98	R&D alliance with Stiefel Laboratories	03/16/98	Earnings report

Number of Confounding Events

Prestige Alliances = 5
 Regional Alliances = 17
 PII/III trials = 17
 Discovery/PI trials = 9
 Total = 48

EVENTS EXCLUDED DUE TO LACK OF ESTIMATION WINDOW DATA

(Estimation window = -20 to -160 days prior to event day 0)

Company	Event Type	Event Date (month/day/year)	Details of Event
Alizyme	Regional Alliance Gain	06/11/96	R&D alliance with Oxford Molecular (obesity)
British Biotechnology	Phase II/III Trials	05/21/96	Marmistat passes PII trial
British Biotechnology	Phase II/III Trials	06/20/96	Marmistat enters PIII trials
Cambridge Antibody Technology	Prestige Alliance Gain	01/08/97	R&D alliance with Eli Lilly
Cambridge Antibody Technology	Discovery/PI Trials	12/15/97	Unveils ProAb discovery technology
Cambridge Antibody Technology	Discovery/PI Trials	08/08/97	Eye disease PI trial begins
Cantab Pharmaceuticals	Prestige Alliance Gain	03/18/97	R&D alliance with Glaxo-Wellcome (Herpes vaccine)
Cantab Pharmaceuticals	Prestige Alliance Gain	07/19/96	R&D alliance with SmithKline Beecham Biologics (vaccine)
Cantab Pharmaceuticals	Discovery/PI Trials	07/15/96	Begin DISC trials
Celltech	Prestige Alliance Gain	02/01/96	R&D alliance with Merck
Celltech	Phase II/III Trials	02/02/96	Asthma drug fails PII trials
Celltech	Phase II/III Trials	01/26/96	Septic Shock drug passes PII trial
Celsis International	Regional Alliance Gain	05/18/96	R&D alliance with Millipore (rapid microbiology)
Chiroscience	Regional Alliance Gain	03/05/96	R&D alliance with Knoll (BASF)
Oxford Asymmetry	Prestige Alliance Gain	02/17/98	R&D alliance with Bayer
Oxford Asymmetry	Regional Alliance Gain	08/07/98	R&D alliance with Monsanto
Oxford Asymmetry	Regional Alliance Gain	08/26/98	R&D alliance with Vertex Pharmaceuticals (identification of lead compounds)
Oxford Asymmetry	Regional Alliance Gain	10/30/98	Ares-Serono granted access to compound library (fees and royalties)
Oxford Glyco Sciences	Prestige Alliance Gain	04/06/98	R&D alliance with Pfizer (Proteomics diagnostics)
Oxford Glyco Sciences	Regional Alliance Gain	01/13/98	R&D alliance with Incyte (includes technology transfer)

Company	Event Type	Event Date (month/day/year)	Details of Event
Oxford Glyco Sciences	Regional Alliance Gain	09/22/98	R&D alliance with Pioneer Hi-breed (agricultural Proteomics)
Oxford Glyco Sciences	Phase II/III Trials	06/10/98	Orphan drug designation for OGT 918 in Phase I/II
PolyMASC	Regional Alliance Gain	06/03/96	R&D alliance with Hydro Med Sciences (cancer vaccine)
Powderject	Prestige Alliance Gain	09/10/97	R&D alliance with Boehringer Mannheim
Powderject	Regional Alliance Gain	12/11/97	R&D alliance with InSite Vision (drug delivery)
Proteus International	Regional Alliance Gain	03/29/96	R&D alliance with MLL Laboratories (prostate and breast cancer)
Shield Diagnostics	Regional Alliance Gain	01/09/96	R&D agreement with Surface Active
Vanguard Medica	Phase II/III Trials	11/19/96	PIII migraine drug (VML 251) trials commence
Xenova	Prestige Alliance Gain	01/28/97	R&D alliance with Bristol Meyer Squibb
Xenova	Prestige Alliance Gain	03/20/97	Compound library development deal with Zeneca
Xenova	Discovery/PI Trials	05/12/97	PI cancer trial to begin

Number of Events Excluded due to lack of Estimation Period Data

Prestige Alliances	= 10
Regional Alliances	= 11
PII/III trials	= 6
Discovery/ PI trials	= 4
Total	= 31

FAILURE EVENTS

Company	Event Type	Event Date (month/day/year)	Details of Event
Biocompatibles	Prestige Alliance Loss	09/10/97	J&J announce that expected alliance will not proceed
British Biotechnology	Phase II/III Trials	12/16/98	Drops Marmistat from Phase III trial
Celltech	Prestige Alliance Loss	05/20/97	Bayer alliance collapses after failure of PIII trial (Septic Shock)
Celltech	Phase II/III Trials	05/20/97	Failure of PIII septic shock trial (Bayer alliance terminated)
Medeva	Phase II/III Trials	06/02/98	FDA refuses marketing application for AD 32
Quadrant Healthcare	Discovery/ Phase I Trials	10/02/98	Abandons development of anti-viral drug Aciclovir (Confound: acquisition of Andris Group)
Scotia Holdings	Regional Alliance Loss	11/27/98	Boehringer Ingelheim cancels licensing agreement
Scotia Holdings	Prestige Alliance Loss	02/27/96	Alliance with Pharmacia Upjohn terminated.
Scotia Holdings	Phase II/III Trials	12/23/97	EMA permanently blocks approval of Tarbetic
Scotia Holdings	Phase II/III Trials	03/12/97	UK medical authorities reject approval of Tarbetic
Vanguard Medica	Prestige Alliance Loss	05/14/98	Negotiations with SmithKline Beecham for marketing deal fail.
Vanguard Medica	Phase II/III Trials	12/09/98	Failure of PII kidney drug trial (confound: 3M alliance)

Number of Failure Events

Prestige Alliances = 4
 Regional Alliances = 1
 PII/III trials = 6
 Discovery/ PI trials = 1
 Total = 12

Appendix Five:

Papers Published and Conference Participation

During the course of my registration as a doctoral student at City University Business School I have written the following academic journal, conference, working and trade journal papers. Parts of this thesis draw upon the work developed in these papers.

ACADEMIC JOURNAL PAPERS

- Mc Namara, P. (1999). Knowledge Based Strategic Alliances and Value Creation: A Study of Biotechnology Firms Quoted on the London Stock Exchange. *Irish Business Administration Review*, Vol. 19/20, pp 99-117.
- Mc Namara, P. and Baden-Fuller, C. (1999). Lessons from the Celltech Case: Balancing Knowledge Exploration and Exploitation in Organisational Renewal. *British Journal of Management*, Vol. 10 (4), pp 291-307.
- Thomson, N. and Mc Namara, P. (1998). Two Way Learning in West/East Mergers and Acquisitions: Short Term and Long Term Viewpoints. *Journal of Eastern European Management Studies*, Vol. 3, No. 2, pp 164-188.

CONFERENCE PAPERS

- Mc Namara, P. and Baden-Fuller, C. (1998). Managerial Processes in the Maintenance of Knowledge Based Competitive Advantage. *Academy of Management Conference*, Business Policy Division, San Diego.
- Mc Namara, P. and Baden-Fuller, C. (1997). Three Traps Facing Knowledge Exploitation in Firms. David Kent (editor), *Eastern Academy of Management Conference Proceedings*, Dublin, pp 16 to 20.
- Mc Namara, P. and Baden-Fuller, C. (1997). Inter-organisational Learning, Strategic Alliances and Value Creation: A Study of the UK Biotechnology Sector. *13th European Group on Organisational Studies Colloquium*, Budapest, Hungary.

Mc Namara, P. and Baden-Fuller, C. (1996). Three Traps Facing the Learning Organisation. *British Academy of Management Conference*, Aston, England.

WORKING PAPER

Mc Namara, P. (1997). Three Risks Attached to Knowledge Intensive Strategies: A Resource Based View and Learning Perspective. *University College Dublin Department of Business Administration Working Paper Series*, BA9701, Ireland.

TRADE JOURNAL PUBLICATIONS

Mc Namara, P. (1999). European Biotech Review: Despite Poor Performance Celltech Shows the Way Forward. *Genetic Engineering News*, Vol. 19 (4), pp 20, 27 and 37.

Mc Namara, P. (1998). British Biotech's Real Problem. *Genetic Engineering News*, Vol. 18 (15), pp 37 and 59.

Mc Namara, P. (1998). European Biotech Companies Struggle to Adjust to Bear Markets. *Genetic Engineering News*, Vol. 18 (20), pp 27, 47, 51 and 52.

Mc Namara, P. (1998). Some Hope and Some Pessimism on the Recovery in European Markets. *Genetic Engineering News*, Vol. 18 (21), pp 27, 28, 53 and 55.